REVIEW

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Electrochemical Characterization and Modulation of Biological Processes

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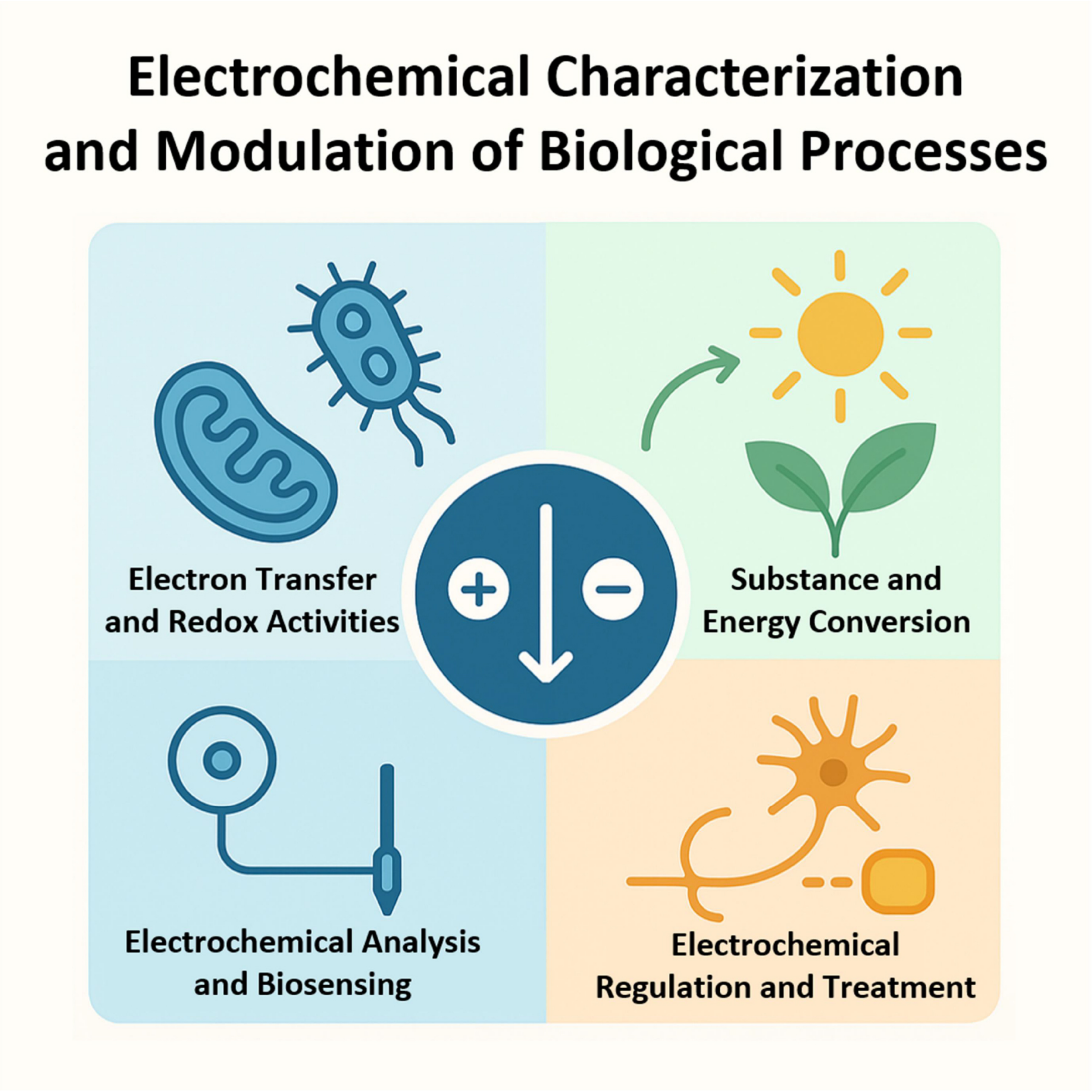
Electrochemical Characterization and Modulation of Biological Processes
Electron Transfer and Redox Activities
Substance and Energy Conversion
Electrochemical Analysis and Biosensing
Electrochemical Regulation and Treatment

Abstract

Electrochemical processes lie at the core of biological function, governing energy transduction, metabolic flux, and molecular signaling. Recent advances in electrochemical science now allow these processes to be probed and controlled with unprecedented spatial, temporal, and chemical resolution. In this review, we present an integrated framework that progresses from fundamental mechanisms to analytical technologies and functional modulation. We begin by outlining electron transfer pathways in mitochondrial respiration, microbial extracellular electron transfer, and DNA- and protein-based charge conduction, followed by the principles of photon-electron conversion in photosynthesis and the central role of redox equilibrium in coordinating cellular responses. We then highlight electrochemical analytical strategies that enable multiscale biological characterization, including biosensing, electrochemical and scanning probe imaging, electrogenerated chemiluminescence detection, and measurements of membrane potentials and neurotransmitter dynamics. Emerging platforms such as flexible biointerfaces, ultramicroelectrodes, and nanopore systems further extend these capabilities to *in vivo* and single-molecule contexts. Finally, we discuss how electrochemical inputs can be used to regulate metabolic pathways, microbial and protein activities, and neural signaling, enabling precision therapeutic and bioengineering applications. Together, these developments establish electrochemistry as a powerful foundation for decoding and directing biological systems.

Keywords: Electrochemical analysis; Single-cell electrochemistry; Biological electron transfer; Photosynthesis; Electrochemical biosensing

1. Introduction

The fundamental biological processes are commonly orchestrated through intricate electron transfer and energy conversion events. For example, cellular respiration uses electron transport chains to drive adenosine triphosphate (ATP) production, photosynthesis converts light into chemical energy, and redox reactions regulate molecular stability and biological function. The disorders in their regulations are central to both normal physiology and disease, thus the methods that can probe and modulate them with precision are increasingly valuable [1, 2]. Electrochemical techniques, marked by high sensitivity, temporal resolution, and versatility, are uniquely suited to examine biology across scales, from individual molecules to whole tissues [3–5]. Compared with optical, genetic, or spectroscopic approaches, electrochemical methods directly couple with electron flow and redox states, making them inherently compatible with the fundamental "electrochemical nature" of biochemical transformations. In this review, we adopt a framework that progresses from fundamental mechanisms to analytical technologies and ultimately to functional modulation.

We firstly introduce the roles of electron transfer in biological energy conversion, including mitochondrial respiration, microbial extracellular electron transfer, and electron shuttling through biomolecular systems [4–7], and discuss photon-electron conversion in photosynthesis, where natural light-harvesting architectures achieve highly efficient charge separation and energy storage [8–11]. The principles of cellular redox regulation [12–15] are subsequently examined, focusing on how dynamic redox equilibria, proton gradients, and membrane potentials govern metabolic flux, signaling networks, and stress responses.

We then highlight electrochemical analytical strategies that enable multiscale characterization of biological processes, including electrochemical biosensing for molecular recognition [16–18], electrochemical microscopic imaging for spatially resolved cellular monitoring [19–21], electrogenerated chemiluminescence for ultra-sensitive readout [22–24], and electrochemical approaches for probing membrane potentials and neurotransmitter dynamics [25, 26]. Emerging platform technologies, such as flexible electrodes that interface with soft tissues [27], ultramicroelectrodes suitable for single-cell environments [28], and nanopore-based systems capable of monitoring individual macromolecular events [29], are emphasized for their capability to capture real-time, *in-situ*, and single-entity biological behavior.

Finally, we discuss how electrochemical inputs can be used to actively modulate biological functions, including regulating metabolic pathway directionality [30–32], altering microbial and protein activities [33, 34], influencing neural communication [35, 36], and enabling therapeutic intervention strategies [37–39]. By integrating fundamental understanding, advanced measurement capabilities, and targeted modulation, electrochemistry provides not only a coherent framework for decoding how biological systems operate, but also a practical toolkit for directing their behavior with precision. This integrated perspective opens opportunities for developing adaptive biointerfaces, engineering programmable cell functions, and guiding therapeutic strategies where metabolic or signaling pathways require controlled intervention. In this way, electrochemistry bridges basic mechanistic insight with translational impact, positioning it as a foundational approach for next-generation bioengineering, medicine, and sustainable biotechnology.

2. Electron Transfer in Biological Processes

Electron transfer (ET) via an electron transport chain (ETC) in cellular respiration is a fundamental process that underlies various phenomena in physics, chemistry, and biology [3]. All cellular energy transformations including photosynthesis, metabolic regulation and redox reactions can be attributed to the ET between different molecules, following a "downhill" trajectory from higher to lower electrochemical potential. The ET system in biological processes is composed of a series of electronic carriers that are embedded in the inner membrane of mitochondria, thylakoid membrane of chloroplasts, or other biological membranes, and their affinity to electrons gradually increases from NADH to oxygen (O_2), which provides the thermodynamic driving force for ET.

The ETC in mitochondria is an entire system featured with electron donors and acceptors, in which hydrogen atoms on metabolites are activated and shed by dehydrogenases to pass through a series of transporters, and finally transferred to activated oxygen atoms to generate water (H_2O). The living cells contain three carriers that receive hydrogen (or electrons) detached from metabolites - NAD^+, $NADP^+$, and FAD. The formed nicotinamide adenine dinucleotide phosphate (NADPH) is a reducing agent for biosynthesis, while NADH and ADH_2 enter the oxidative respiration chain and succinic acid oxidative respiration chain, respectively. These ETCs contain more than 15 components, mainly composed of 4 enzyme complexes (Complexes I, II, III and IV) and 2 mobile electron carriers [1].

In cellular respiration, some compounds, such as carbohydrates, lipids, and proteins, are oxidized to release electrons, protons, and produce ATP. In catabolic pathways, such as glycolysis and citric acid cycle, the oxidation reactions are linked to the reductions of NAD^+ and FAD to NADH and $FADH_2$, respectively. In the glycolysis process, glucose is converted to pyruvate, producing some ATP. Pyruvate is then converted into acetyl coenzyme A to enter the tricarboxylic acid cycle, and electrons are carried by NADH and ubiquinol (QH_2) to cytochrome c oxidase for reducing O_2 to H_2O, while the produced energy is used to pump protons across the inner mitochondrial membrane, setting up a proton gradient as proton-motive force for ATP synthesis.

The ET in biological processes is generally investigated with *in-situ* and *operando* electrochemical methods or coupled with spectrometric and microscopic techniques. They provide structural and electronic information while the energetic state is modulated by the application of a certain potential to the bioentities immobilized on an electrode. For example, a carboxylic acid functionalized hydroquinone has been immobilized on multiwalled carbon nanotube to modify glassy carbon electrode (GCE/MWCNT@H_2Q-COOH) for studying the direct voltammetric ET reaction of unfolded cytochrome c (Cyt c) [6]. It shows well-defined redox peaks corresponding to consecutive one-electron-transfer reactions of H_2Q-COOH/•QH-COOH and •QH-COOH/Q, similar to a membrane-bound ubiquinone and plastoquinone system. The unfolded Cyt c modified electrode, GCE/MWCNT@H_2Q-COOH@Cytc, exhibits a specific and selective bioelectrocatalytic reduction between the redox potentials of QH_2/•QH and Cyt c, biomimicking the biological ETC reaction and redox signaling. Cytochrome c oxidase (CcO) functions as a terminal electron acceptor in mitochondrial and bacterial respiratory chains, driving cellular respiration and transducing the free energy from O_2 reduction into proton pumping. This redox reaction creates a proton motive force across a biological membrane that drives the synthesis of ATP. A recent work combines large-scale quantum chemical DFT calculations with hybrid quantum mechanics/molecular mechanics simulations and atomistic molecular dynamics explorations to find that internal redox changes in CcO create orientated electric fields that sort the protons along the chemical and pumping pathways, while preventing back leakage reactions [4]. These redox triggered electric fields show distinct similarities to other energy-converting enzymes and may be a general principle of enzyme catalysis. Solid-state nanopore sensing approaches have been considered as a robust and promising tool for ET investigation due to their remarkable sensitivity and versatility in single-entity electrochemical measurements [5]. A label-free and noninvasive imaging method has also been developed to measure the ET in microbial cells by imaging the redox reaction of c-type outer membrane cytochromes to obtain the electrochemical activity parameters (formal potential and number of electrons transferred) of multiple individual microbial cells [7]. This method can contribute to the study of ET in various biological and chemical processes.

The understanding of the behaviors of molecules involved in the biological ET processes, such as redox proteins, nucleic acids, organelles or living microbes, at the electrode surface via protein film or monolayer voltammetry, or bioelectrochemistry approach can provide us with much insight into life processes, and is also important for the development of bioelectrocatalysis for biofuel cells, biosensors and a variety of bioelectrochemical devices [40]. This mode of charge transfer requires distances of <1.5 nm, hence direct immobilization with favorable special orientation, and energy match between the redox potential of the active site and the electrode polarization. Great efforts have been made to improve the direct electron transfer (DET) and mediated electron transfer (MET) by modifying the electrodes and optimize biotic/abiotic interfaces for studying the heterogeneous ET at bioelectrode interfaces, the intramolecular charge transfer either through electron transport or electrostatic channeling, and the extracellular charge transfer. A combination of rational interface design, high-resolution characterization, and multiscale simulations emerges as a strategy to promote understanding and utilization of electron transport mechanisms.

The ET processes of nucleic acids are related to genetic repair mechanisms, replication, and regulatory functions, which involve the large set of multiple and apparently conflicting mechanisms rooted in structural and functional peculiarities, such as mediation by π-stacking interactions, hopping through aromatic units of the nucleobases, long-range tunneling, and transport through the outer sphere of the solvated phosphodiester backbone [41]. For example, early results suggested that the ET events should be limited to small distances, close to that in proteins due to high predicted potential barriers, but years later the voltammetric study showed the electron transport over 34 nm in 100-mer onto gold chips [42], which opened great interest in the context of molecular wires.

Theoretically, the direct ET process between metalloproteins (enzymes), including cytochromes, blue copper proteins and ferredoxins, and electrodes is closer to the original model of biological redox systems, laying the foundation for revealing the mechanisms of biological ET processes. Therefore, the ET process involving metalloproteins has been widely reported [43]. The redox potentials of these proteins are related to many factors such as the identity of the metal, the structure and geometry of its coordination sphere, the structure of the protein itself, the extent of the exposure of the metal complex to solvent, and even their modifications. The EC process accompanied with protein modifications in signal pathways has attracted extensive attention [12]. The study of electronic behavior in signal pathways can be performed with electrochemical, photoelectrochemical and electrochemiluminescence methods. For example, the electrochemical analysis of protein kinase (PK) activity involved in protein phosphorylation by synthetic probes immobilized on the electrode surface was achieved via the specifically binding to phosphorylated peptides [13], a visible-light-excited photoelectrochemical biosensor for the detection of protein phosphorylation was proposed by linking DNA-conjugated gold nanoparticles to phosphorylated peptide fixed on TiO_2/ITO electrode [14], and an Au&Pt@UiO-66 probe was also constructed for electrochemiluminescence signal amplification detection of PK activity [15].

In a diversity of microorganisms, including bacteria and fungi, the ET from the cells to the environment is crucial for generating energy for their growth and maintaining the intracellular redox balance. It involves the direct contact of the cells with the external electron acceptor, which is usually promoted by redox proteins in the microbial outer cellular membrane, such as cytochromes, or is mediated by redox molecules naturally excreted by the cell (metabolites) or exogeneous redox mediators [44]. The outer-membrane c-type cytochromes (OM c-Cyt) exhibit the great importance as the ET catalyst for electrochemically active bacteria (EAB) to reduce the extracellular acceptors [45]. These c-Cyts adopt hemes composed of porphyrin rings and iron atoms as the redox active center for interfacial ET catalysis [46]. The extracellular ET has demonstrated its multiple electron shuttles in waterborne aeromonas hydrophila, which produces both flavins and 2-amino-3-carboxy-1,4-naphthoquinone (ACNQ) as electron shuttles to accelerate the ET for bioreduction of pollutants (Fig. 1) [47].

3. Photon-electron Energy Conversion in Biological Photosynthesis

Photosynthesis is defined as the process by which plants, algae, and certain bacteria convert light energy into organic compounds from carbon dioxide (CO_2) and H_2O, releasing oxygen as a byproduct [48]. This process is one of the most critical energy conversion mechanisms on Earth, fundamentally involving the transformation of photon energy into chemical energy, thereby driving carbon fixation and biomass synthesis. The conversion of photon-electron energy is a central component of the light reactions in photosynthesis, primarily occurring on the thylakoid membranes of chloroplasts. The transfer of energy between photons and electrons during biological photosynthesis is considered one of the foundational elements for the emergence of life [49–51]. This review examines the molecular mechanisms and research advancements related to photon-electron energy conversion in biological photosynthesis, with a focus on the historical development of photosynthesis research, photon capture and electron transfer, crystal structure analysis, and studies inspired by photosynthesis.

3.1. Historical development of photosynthesis research

In 1771, Joseph Priestley conducted an experiment in which he placed a plant and a mouse in a sealed container exposed to light, discovering that the

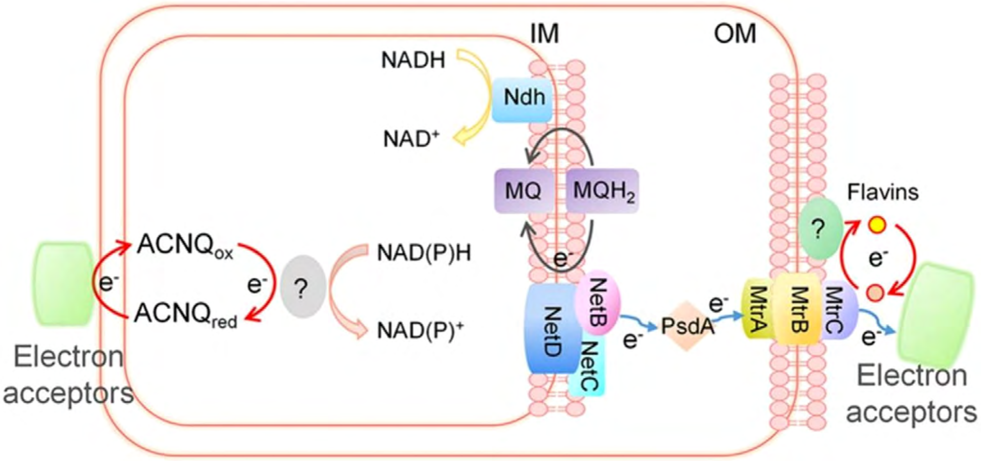

Fig. 1. Schematic of the proposed indirect EET mechanism of Aeromonas hydrophila. Flavins can act as electron shuttles to transfer electrons from cells via the Mtr-like respiratory pathway-mediated mechanism. However, the electron shuttle activity of ACNQ may involve the redox reactions that occur inside the cell rather than the canonical cytochrome-mediated mechanism. IM, inner membrane; OM, outer membrane. Reproduced with permission of Ref. [47].

mouse could survive for an extended duration. This experiment is regarded as one of the first instances in which humans empirically recognized the occurrence of photosynthesis. Subsequent research revealed that a specific component within plant leaves utilizes light energy to convert absorbed CO_2 and H_2O into carbohydrates while releasing oxygen. In 1954, Melvin Calvin and his colleagues elucidated the intricate pathway of carbon fixation in photosynthesis, naming it the Calvin-Benson-Bassham (CBB) cycle [52]. This discovery established the foundational theoretical framework for understanding the dark reactions of photosynthesis. In 1957, Emerson and his team discovered that not only long-wavelength red light at 680 nm, but also relatively shorter-wavelength red light at 660 nm, could activate photosynthesis. This finding laid the foundation for the dual-light system theory (Photosystem I and Photosystem II, PSI and PSII for short) in contemporary photosynthesis research. The year 1988 represented a pivotal moment in photosynthesis research, as the Nobel Prize in Chemistry was awarded to Johann Deisenhofer, Robert Huber, and Hartmut Michel for successfully resolving the three-dimensional (3D) structure of the bacterial photosynthetic reaction center and elucidating its reaction mechanism. This breakthrough ushered in a new era of photosynthesis research, leading to a surge in structural biology studies that provided detailed insights into the ET mechanisms and chemical processes underlying the enigmatic phenomenon of photosynthesis (Fig. 2).

In 2001, Jordan and colleagues first resolved the 3D structure of PSI from cyanobacteria, revealing its highly efficient light-driven ET mechanism. This represented a significant advancement in understanding the structural biology of photosynthesis and laid the groundwork for subsequent studies on the function and regulation of PSI [8, 9]. In 2004, Liu and his team elucidated the primary crystal structure of the light-harvesting complex in PSII from spinach [10, 11], providing critical insights that enhanced the understanding of PSI's function and regulation. At this stage, several critical components of photosynthesis research had received preliminary reports, including

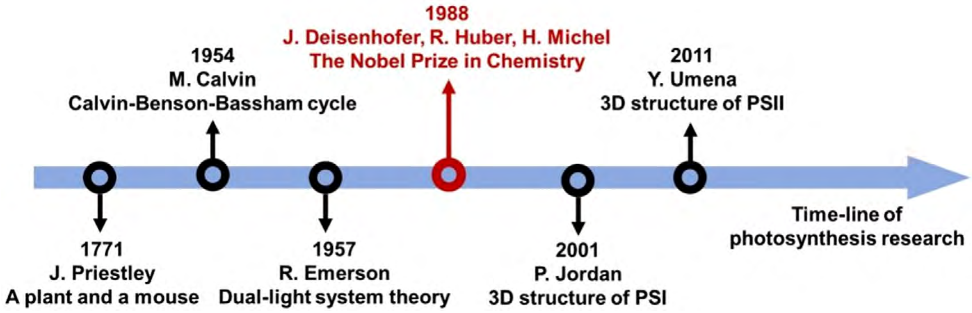

Fig. 2. Timeline for the development of fundamental research in photosynthesis.

the light reactions (PSI and PSII), dark reactions (CBB cycle), ET pathways, and key proteins involved in the process. Further detailed investigations have increasingly unveiled the structure and function of specific participating proteins, such as the finding by William and colleagues that the RuBisCO enzyme exhibits oxygenase activity [53]. In recent years, advancements in cryo-electron tomography and the integration of artificial intelligence-assisted structural biology tools, such as AlphaFold, have enabled researchers to gradually elucidate numerous intricate protein structures. It is conceivable that one day, the complex photosynthetic systems could be precisely characterized, potentially allowing for energy acquisition from sunlight to become capabilities not exclusive to plants or microorganisms.

3.2. Photon capture and electron transfer

The process of photosynthesis involves the interaction of two distinct photochemical phases, specifically photon capture and a multi-step ET process mediated by various proteins. In simpler terms, plants and microorganisms capture photon energy via photosynthetic pigments, such as chlorophyll and carotenoids, which excite electrons to higher energy states. This process primarily occurs within the core complexes of PSII and PSI, which facilitate the photolysis of water and the generation of NADPH, respectively. PSII absorbs photons at a wavelength of 680 nm, facilitating the dissociation of water molecules into oxygen, protons, and electrons. Subsequently, PSI, which absorbs at 700 nm, transfers electrons to ferredoxin, ultimately leading to NADPH production. Once NADPH is generated, the roles of the light reactions in photosynthesis are fulfilled. NADPH, the final product of the light reactions, serves as a crucial reducing agent that participates in the dark reactions (CBB cycle) for CO_2 fixation. Through a series of cyclic reactions, glucose is ultimately synthesized [49].

Specifically, organisms capable of photosynthesis possess two types of photosystems (PSI and PSII), each comprising a reaction center (P680/P700) and peripheral light-harvesting pigment-protein complexes (LHCs), such as LHCII. The pigments within these complexes, including chlorophyll a, chlorophyll b, and carotenoids, absorb light energy and transfer it to the reaction centers via resonance energy transfer (non-radiative energy transfer). Light energy is absorbed by P680 in the PSII reaction center, exciting it to the state P680* (the high-energy state). P680* then transfers a high-energy electron to the primary electron acceptor, pheophytin, resulting in charge separation ($P680^+/Pheo^-$). Subsequently, $P680^+$ retrieves an electron from the manganese cluster (Mn_4CaO_5) through the oxidation of H_2O, producing O_2, protons (H^+), and electrons (e^-). The electrons from PSII are then transferred through QA (the primary electron acceptor) and QB (the secondary electron acceptor) to the plastoquinone (PQ) pool, where PQ is reduced to plastoquinol (PQH2). PQH2 is subsequently oxidized in the b6/f complex, releasing two protons into the thylakoid lumen and transferring electrons to plastocyanin (PC) through the "Q cycle." Electrons from PC are then transferred to P700 of PSI and subsequently to ferredoxin (Fd), which transfers the electrons to ferredoxin-NADP$^+$ reductase (FNR), ultimately producing NADPH. In addition to the aforementioned direct ET chain, there exists a mechanism referred to as cyclic electron transport. In this process, electrons from Fd are returned to the PQ pool through the PGR5/PGRL1 complex (Fig. 3a). This cyclic electron transport through the b6/f complex generates a proton concentration gradient that drives ATP synthesis. The ATP produced from this cyclic electron transport is utilized for energy consumption in the subsequent dark reactions of the CBB cycle [49].

3.3. Crystal structure analysis

The ET pathways in photosynthesis demonstrate that the photosynthetic reaction systems, Photosystem I (PSI) and Photosystem II (PSII), are the two core protein complexes essential for capturing, transferring, and converting light energy. Research into the structures and functions of PSI and PSII has remained a focal point and challenge in the fields of plant biology and biochemistry. The elucidation of high-resolution structures of PSI and PSII yields critical insights for a deeper understanding of the mechanisms underlying photosynthesis.

Jordan, Adam, and other researchers have demonstrated that PSI consists of multiple subunits, including core reaction center subunits and antenna protein subunits [8, 9]. For instance, in plant PSI, the core reaction center comprises the PsaA and PsaB subunits, along with multiple chlorophyll molecules and iron-sulfur clusters serving as cofactors. Antenna proteins, such as LHCI, encircle the core reaction center, forming a specific arrangement that optimizes light capture. This precise molecular composition and spatial arrangement help elucidate how PSI efficiently captures and transmits light energy. The crystal structure enables clear visualization of the components and arrangement of the ET chain within PSI. For example, P700, the primary electron donor of PSI, has had its distances and interaction modes with surrounding chlorophyll molecules and iron-sulfur clusters (such as FX, FA, and FB) precisely elucidated. This detail aids in revealing how electrons are

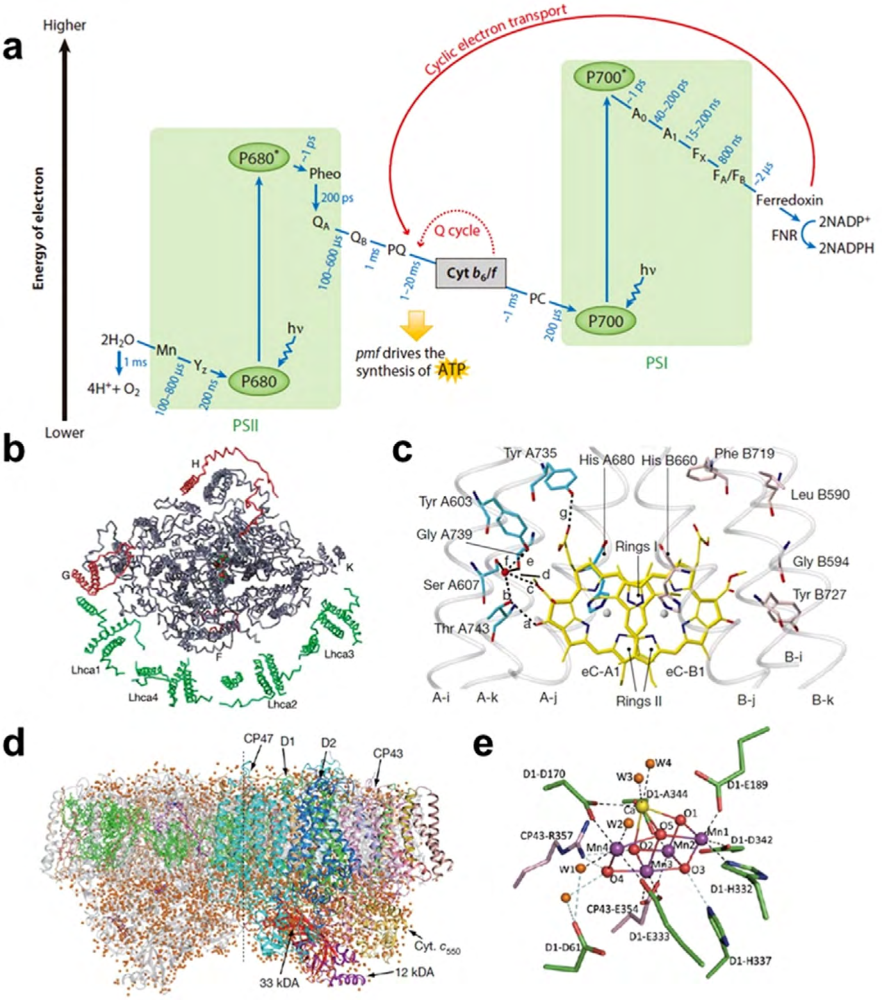

Fig. 3. Electron transfer pathways in photosynthesis and structural characterization of key protein complexes. (a) Electron transfer pathway in photosynthesis [49]. (b) Crystal structure of the PSI complex [9]. (c) Crystal structure of P700 [8]. (d) Crystal structure of the PSII complex. (e) Crystal structure of the manganese cluster (Mn_4CaO_5), a key component in photosystem II [11]. Reproduced with permission of Refs. [8], [9], [11] and [49].

transferred from P700 through a series of cofactors, ultimately reaching ferredoxin (Fd), demonstrating the efficiency of energy conversion in this process (Fig. 3b). The crystal structure also illustrates the tight binding mode between PSI and the antenna protein LHCI. LHCI interacts with the PSI core reaction center through specific structural domains, effectively transferring captured light energy to the PSI reaction center (Fig. 3c). Understanding these interactions is crucial for elucidating the mechanisms of light energy transfer within the PSI complex and enhancing the efficiency of light energy utilization.

The crystal structure analysis of PSII conducted by Liu and colleagues revealed its highly complex subunit composition, including core reaction center subunits (D1 and D2), antenna proteins (CP47 and CP43), cytochrome b559, and several peripheral subunits [10, 11]. These subunits create a specific spatial arrangement that underpins the functionality of PSII. Understanding the precise positions and interactions of these subunits is crucial for elucidating PSII assembly, stability, and functional regulation. Within the crystal structure, researchers identified key sites involved in ET and water oxidation. The arrangement and characteristics of chlorophyll molecules within the D1 and D2 subunits, tyrosine residues (YZ and YD), and the water-oxidizing complex composed of manganese, calcium, and chloride were accurately determined. This information facilitates in-depth studies of the ET pathway from water molecules to plastoquinone (PQ) and elucidates the redox changes of the manganese cluster during water oxidation and the mechanisms of oxygen generation. Unlike PSI, PSII is more susceptible to photodamage during photosynthesis, necessitating the development of protective mechanisms (Fig. 3d). The crystal structure analysis revealed that this photoprotection arises from specific peripheral subunits that adjust their conformation under light stress conditions to mitigate excessive light energy absorption, thus protecting PSII from damage. The crystal structure of PSII provides a crucial reference model for studying its functionality and regulatory mechanisms. With this structural information, scientists can design protein mutagenesis experiments and develop novel spectroscopic detection techniques to further investigate PSII's behavior and regulation under various physiological conditions (Fig. 3e). Moreover, these structural insights also lay the theoretical foundation for the artificial simulation of the water-oxidation process during photosynthesis and the design of new photocatalytic materials.

In the field of photosynthesis research, crystal structure analysis not only elucidates the precise molecular composition, spatial arrangement, and ET pathways of PSI and PSII, but also provides critical insights into their mechanisms of light energy conversion, evolutionary adaptability, and photoprotective strategies. With ongoing advancements and applications in crystallography, it is anticipated that higher resolution and more comprehensive structural information regarding PSI and PSII will be achieved in the future. This progress will further enhance the exploration of photosynthesis, and offer new strategies and methods to tackle global challenges related to energy and the environment.

3.4. Research inspired by photosynthesis

In exploring biological photosynthesis, researchers not only have marveled at the intricate designs of nature but also developed numerous research directions inspired by its principles. These include, but are not limited to: studies on the diverse structures and mechanisms of photosynthesis; research on enzyme-catalyzed processes that mimic photosynthetic systems; investigations into semi-artificial photosynthetic systems; and studies on synthetic biology aimed at regulating photosynthesis. Through these investigations, researchers are driven to explore and harness the intrinsic photonic and electronic energy transfer processes of photosynthesis. By modulating or altering the pathways of energy transfer, they aim to achieve research objectives across chemistry, engineering, and biology. In this review, we summarize several representative studies; indeed, research inspired by photosynthesis continues to expand into various fields.

In studying the various structures and mechanisms of biological photosynthesis, Li et al. reported the structure of a supercomplex formed by maize Photosystem I (PSI) in association with Light-Harvesting Complex I (LHCI) and Light-Harvesting Complex II (LHCII) [54] (Fig. 4a, b). They utilized cryo-electron microscopy to reveal a high-resolution structure at 3.3 Å. The findings revealed the arrangement of chlorophyll molecules in both PSI-LHCI and LHCII, and how they regulate the phosphorylation of LHCII under varying light conditions to balance energy input between the two photosystems. This mechanism may offer insights into the molecular basis of state transitions during photosynthesis.

In enzyme-catalyzed studies mimicking photosynthetic systems, Zhang et al. reported the synthesis of a Mn_4Ca cluster that mimics the structure and function of the oxygen-evolving center (OEC) in photosynthesis [55]. The synthesized Mn_4Ca cluster consists of a Mn_3CaO_4 cube and a "hanging" manganese ion connected by two bridging oxygen atoms, structurally resembling the natural OEC (Fig. 4c, d). Electrochemical cyclic voltammetry and electron paramagnetic resonance (EPR) characterizations indicated that the synthesized Mn_4Ca cluster exhibits redox potentials and magnetic properties similar to those of the natural OEC. Zhang's research provides new tools and insights for investigating water oxidation mechanisms in photosynthesis and for developing artificial photosynthetic catalysts.

In semi-biological photosynthetic system research, Yang et al. have focused on employing microorganisms with photosynthetic capabilities to reduce CO_2 and produce bulk chemicals and hydrogen through semi-biological photocatalytic reactions [51]. Recently, they developed a novel bipolar photosynthetic device that utilizes red light (740 nm) to facilitate CO_2 multicarbon conversion at the biophotoanode and glycerol oxidation at the photoanode. This device consists of efficient photosynthetic microorganisms (Sporomusa ovata) combined with silicon nanowire biophotoanodes and platinum-gold-loaded silicon nanowire photoanodes (Fig. 4e). Under low-intensity red light (20 $mW \cdot cm^{-2}$), the device operates without applied bias, achieving a Faradaic efficiency of approximately 80% for both cathode and anode products. By utilizing a methanol-adapted S. ovata strain, the conversion rate of CO_2 was enhanced, leading to improved solar-to-chemical conversion efficiency of multicarbon products under unbiased conditions, effectively converting CO_2 into multicarbon products and simultaneously transforming organic compounds into high-value-added chemicals [56].

In the field of synthetic biology focused on regulating photosynthesis, Milo et al. successfully enabled Escherichia coli to synthesize sugars from CO_2 through metabolic engineering and directed evolution [57]. Specifically, by knocking out certain genes in E. coli (such as gpmA and gpmM), Milo disrupted the glycolytic and gluconeogenic pathways,

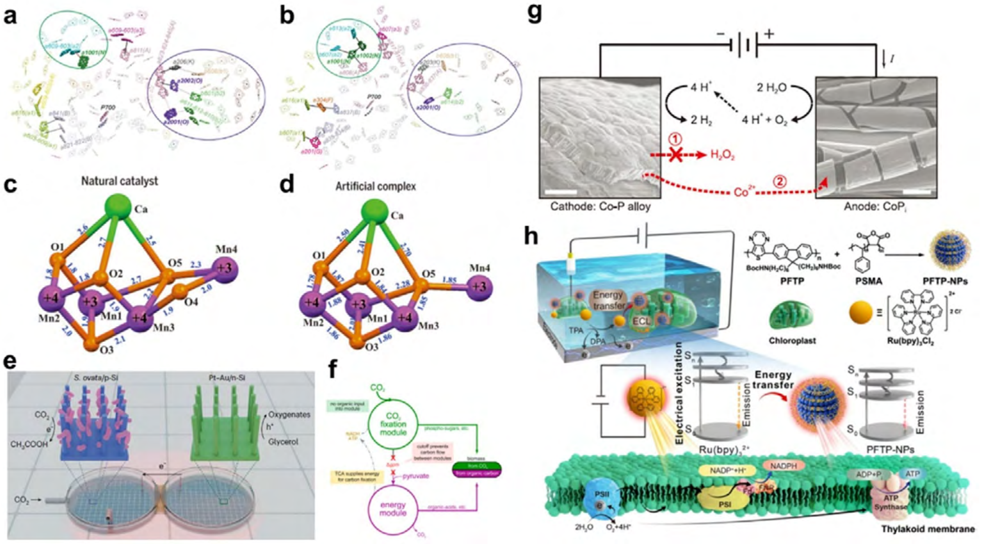

Fig. 4. Typical researches inspired by photosynthesis. (a) Distribution of chlorophylls within the PSI-LHCI-LHCII supercomplex at the stromal layer [54]. (b) Chlorophylls at the luminal layer. (c) Mn_4CaO_5 core of the native OEC [55]. (d) Mn_4CaO_4 core of $[Mn_4CaO_4(ButCO_2)_8(ButCO_2H)_2(py)]$ (But, tert-butyl; py, pyridine) [55]. (e) Schematic of a bias-free photochemical diode device consisting of a photocathode and a photoanode separated by a bipolar membrane under red light irradiation. Magnified illustrations of a p-type SiNW biophotocathode (blue) and an n-type SiNW photoanode (green) show the reaction interface of the two photoelectrodes. S. ovata (pink) was used as the cathodic microbial catalyst for the CO_2RR and co-sputtered Pt-Au was used as the anodic catalyst for the GOR [56]. (f) Decoupling energy production and carbon fixation in E. coli to achieve hemiautotrophic growth [57]. (g) Reaction diagram and scanning electron microscopic images for Co-P alloy cathode and CoPi anode, the main water-splitting reaction is shown in black; the side reactions that yield toxicants are in red. Scale bars, 10 mm [58]. (h) Illustration of the strategy that utilizes ECL and PFTP-NPs to activate and regulate chloroplast photosynthesis [59]. Reproduced with permission of Refs. [54–59].

decoupling energy acquisition from biomass synthesis (Fig. 4f). This metabolic rearrangement allowed E. coli to synthesize sugars from CO_2 via the non-native Calvin-Benson-Bassham (CBB) cycle. They subsequently employed continuous culture (chemostat) techniques to drive the evolution of E. coli expressing recombinant RuBisCO and PRK. Under selective pressure, the bacteria gradually adapted to a growth mode in which they synthesized sugars from CO_2 via the CBB cycle.

Inspired by the mechanisms of natural photosynthesis, electrochemical techniques have also advanced electrocatalysis, biosynthesis, and other related fields [58–60]. For example, the ‘water-splitting-biosynthesis hybrid system’ reported by Liu et al. in *Science* [58] exemplifies the concept of electrochemically modulating photosynthetic processes. In that work, a low cell voltage of 2.0 V in neutral water was used to drive a Co-P alloy cathode and a self-healing CoPi anode, enabling highly efficient H_2 production (Faradaic efficiency >99%) with negligible biological toxicity. The generated H_2 was immediately assimilated by autotrophic bacteria (*Ralstonia eutropha*) attached to the electrode surface and served as the reducing equivalent to convert low-concentration CO_2 (including air-level 400 ppm) into biomass, polyhydroxybutyrate (PHB), or C_3-C_5 alcohols. The electrochemical-to-chemical energy conversion efficiency reached up to 54%, and when coupled to photovoltaics the overall solar-to-chemical efficiency was approximately 10%, surpassing the photosynthetic efficiency of natural plants and microalgae. The system operated stably under intermittent (day-night) power input, demonstrating that electrochemical supply of controlled reducing equivalents can overcome the electron-transport and energetic bottlenecks inherent to natural photosynthesis, and enable a novel ‘electro-photo-bio’ hybrid photosynthetic paradigm. Wang et al. [59] developed an electrochemiluminescence (ECL)-based, conjugated-polymer *in-situ* light-delivery strategy that excites $Ru(bpy)_3^{2+}$/TPA at a low driving potential of 1.2 V to produce sustained emission centered at 620 nm. By embedding PFTP nanoparticles (emission about 660 nm) for secondary wavelength conversion, the system increased spinach chloroplast ATP and NADPH production by 466% and 200%, respectively, with a quantum efficiency of 1.48%-an 8% improvement over a light-emitting diode (LED) control. The ECL-polymer composite can be 3D-printed into arbitrary hydrogel geometries, enabling light-window-free and fiber-free, spatiotemporally controllable ‘electro-light-photosynthesis’ coupling. This approach provides a directly deployable electrochemical modulation paradigm for precision agriculture and artificial photosynthesis.

Except the representative cases mentioned above, numerous researchers have made significant contributions to the photonic and electronic energy transfer processes in photosynthesis. These studies have had a profound impact on various fields, including biology, materials science, catalysis, and chemical engineering. Whenever reflecting on these findings, people are amazed by the intricate pathways that nature has created for transforming light energy into chemical energy, essential for the emergence of complex life forms.

4. Mechanisms of Cellular Redox Processes

Intracellular redox balance, a consequence of the battle between reactive oxygen species (ROS) / reactive nitrogen species (RNS) generation and scavenging systems, is one of the important factors in regulating cell behavior and function [61–63]. Any disruption of this balance can lead to oxidative stress, resulting in biological damages and various pathological conditions. Thus, cells are equipped with complex antioxidant defense systems to prevent, delay, or remove oxidative damage to the target biological molecule and the cell itself. In recent decades, the nanoelectrochemical method has demonstrated its excellent advantages in terms of both high spatiotemporal resolution and the capacity for real-time monitoring of intracellular biomolecules within individual living cells to elucidate the mechanisms of cellular redox processes.

4.1. Detection of reactive species

The characterization of ROS/RNS concentrations and their dynamic fluctuations in living cells has driven the development of novel electrodes and highly sensitive detection techniques [64–69]. A critical advancement in this field was achieved by Mirkin and coworkers [70], who pioneered the use of nanoelectrodes for electrochemical analysis of electroactive biomolecules within single living cells. By integrating scanning electrochemical microscopy (SECM) for precise cellular localization, they achieved detection of redox-active species in individual cells with nanoscale spatial resolution, establishing a foundational approach for single-cell electrochemical studies. In another seminal study, Jiang and colleagues [71] further reduced the ROS detection limit to 1 nmol·L^{-1}. This improved detection sensitivity guarantees the spatial investigation of the ROS distribution in a 3D cell sphere, revealing significant differences in oxidative stress between 3D and 2D cell models, providing direct evidence for the metabolic differences between 2D and 3D cells (Fig. 5a).

Organelles and the cytosol interact through intricate mechanisms to maintain efficient and orderly redox processes, which are fundamental to cellular life activities [72]. To avoid interference from other molecules in the cytosol and achieve *in-situ* dynamic monitoring of ROS in single mitochondria, Liu et al. [73] used a rapid click chemistry reaction to capture single target mitochondria at the pipette tip. Dynamic tracking of ROS release from single mitochondria revealed

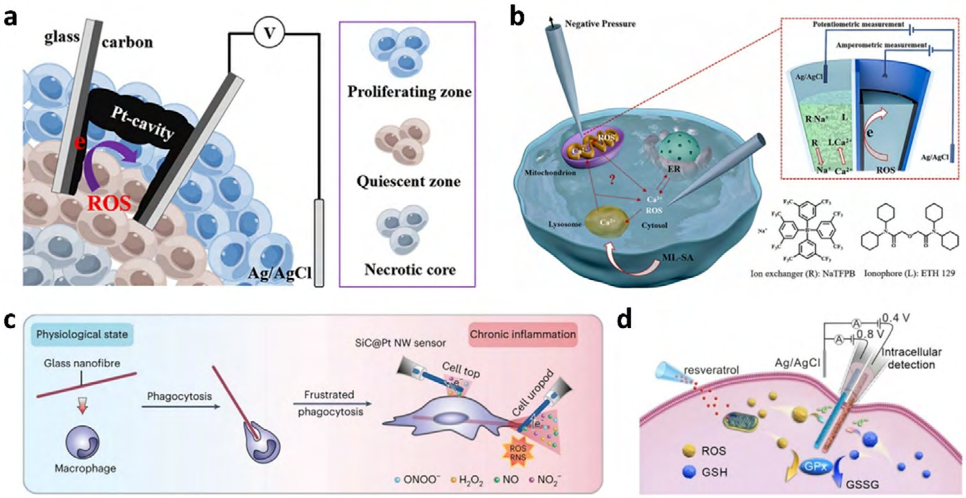

Fig. 5. Spatiotemporally resolved single-cell electrochemistry for quantifying reactive species fluxes. (a) Schematic illustration of the platinized open carbon nanocavity for the analysis of ROS in a single 3D CT26 cell model with a proliferating zone, quiescent zone, and necrotic core [71]. (b) Schematic representation for the simultaneous electrochemical analysis of Ca^{2+} and ROS in a single mitochondrion and the surrounding cytosol [74]. (c) Schematic diagram for differentiating the ROS/RNS released at different loci of the macrophage surface and quantifying their fluxes [75]. (d) Schematic illustration of real-time monitoring of the intracellular ROS and reduced glutathione induced by Resveratrol [76]. Reproduced with permission of Refs. [71], [74], [75] and [76].

a unique "ROS-induced ROS release" (RIRR) mechanism. They investigated the mitochondrial-level details of the RSL3-induced ferroptosis pathway, showing that RSL3 induces ferroptosis by acting on (glutathione peroxidase 4) GPX4 in the cytosol rather than in mitochondria. This finding provides deeper insights into the molecular mechanisms of ferroptosis. Moreover, simultaneous monitoring of molecular trafficking dynamics between individual organelles and the surrounding cytosol with high spatiotemporal resolution is essential for understanding their biological functions. An established methodological approach involves the integration of two independent nanosensors within a θ-nanopipette configuration [74]. The results revealed that lysosomal Ca^{2+} directly triggers mitochondrial ROS bursts via RIRR during mucolipin-specific agonist-induced (ML-SA-induced) autophagy, while mitochondrial ROS reciprocally activates transient receptor potential mucolipin 1 (TRPML1) channels to drive secondary Ca^{2+} waves, uncovering a redox-Ca^{2+} positive feedback loop governing interorganellar communication (Fig. 5b).

Multiple ROS/RNS exist simultaneously in cells, and it is necessary to distinguish them for more accurate dynamic analysis. Expanding the methodological toolbox for single-cell analysis, Mirkin and colleagues [77] pioneered an integrated resistive pulse sensing-electrochemical detection system that achieved quantitative determination of four critical ROS/RNS species in human mammary cells, resolving their spatiotemporal dynamics and production kinetics at subcellular resolution. To detect individual organelles, Hu et al. [78] stimulated RAW 264.7 macrophages with interferon-gamma/lipopolysaccharide (IFN-γ/LPS) to simulate *in vivo* activation, causing lysosomal swelling. Through real-time monitoring of key ROS/RNS species ($ONOO^-$, H_2O_2, NO, and NO_2^-) dynamics within individual phagolysosomes using a four-step chronoamperometric method, significant heterogeneity in their production kinetics was uncovered, highlighting the intricate regulatory mechanisms underlying phagocytosis. Building on this, Huang and coworkers [79] combined potential differentiation and intracellular vesicle impact electrochemical cytometry (IVIEC) to detect the rapid (<1 ms) ROS/RNS homeostasis regulation mechanism exists in phagolysosomes. This work revealed that phagolysosomes in macrophages dynamically regulate ROS/RNS production via the coordinated distinct enzymatic mechanisms, NADPH oxidase (NOX, which mainly generate superoxide ions) and nducible nitric oxide synthases (iNOS, which mainly generate nitric oxide), to maintain redox homeostasis during pathogen clearance. Furthermore, to bridge the gap between single-cell behavior and tissue damage, Qi et al. [75] monitored the flux and dynamics of reactive species release during the frustrated phagocytosis of glass nanofibres by single macrophages. The results showed significant temporal differences in ROS/RNS release during various stages of phagocytosis. This continued massive leakage of ROS/RNS damages peripheral cells, and eventually translates into chronic inflammation and lung injury (Fig. 5c).

4.2. Detection of antioxidants

To maintain intracellular redox balance, cells possess a sophisticated antioxidant defense system. This system comprises various antioxidant enzymes (e.g., superoxide dismutase (SOD), glutathione peroxidase(GPx)) and antioxidant molecules (e.g., glutathione (GSH), vitamin C, and vitamin E) [80]. GSH is the most critical small-molecule antioxidant in cells, directly neutralizing ROS, maintaining redox homeostasis, and protecting cells from oxidative damage. Zhao and colleagues [81] demonstrated that a nanocapillary-based sensing platform, with an immobilized organic molecular probe on the inner capillary wall, enables GSH quantification in single cells through characteristic ion current rectification changes upon probe-GSH interaction. This approach allowed precise mapping of GSH distribution at subcellular resolution in single cells, revealing distinct spatial heterogeneity and dynamic fluctuations in response to physiological stimuli such as glucose deprivation. In a series of studies, a controllable and stable assembly platform for multiple biomimetic molecular catalysts, such as metal phthalocyanines and metal porphyrins, was firstly developed on conductive nanowires surfaces by Wu et al. [82]. Through H_2O_2-induced oxidative stress simulation, this work directly captured dynamic fluctuations in GSH-mediated redox homeostasis during cellular stress responses. To provide novel insights into the GSH antioxidant system and redox imbalance physiology, the dual-wire nanosensor (DWNS) has been successfully applied for the simultaneous, real-time monitoring of both drug-induced intracellular ROS bursts and the rapid antioxidant process of the GSH system [76]. The simultaneous assay results showed that the GSH system, particularly glutathione peroxidase 1 (GPx1), rapidly initiates antioxidant defense within a sub-second time scale upon ROS burst, highlighting its critical role in maintaining redox homeostasis during oxidative stress. However, GPx1-mediated ROS elimination is transient (lasting only a few seconds), while residual ROS persist and may be cleared by alternative antioxidant pathways (Fig. 5d).

Electrochemical methods have become indispensable for elucidating cellular redox mechanisms by providing the context-specific resolution required to decipher redox signaling dynamics at molecular scales. By leveraging advanced nanoelectrodes and innovative sensing platforms, researchers can now monitor dynamic changes in reactive species (e.g., ROS/RNS) and antioxidants (e.g., GSH) at subcellular levels in real time. These techniques have elucidated critical mechanisms, such as organelle-specific redox signaling, interorganellar communication, and rapid antioxidant responses, while also revealing heterogeneity in redox states across cell models. Overall, nanoelectrochemical methods enable precise modulation of cellular redox homeostasis, providing unique insights into disease pathogenesis and the development of novel therapeutic strategies.

5. Electrochemical Analytical Strategies for Biological Processes

5.1. Electrochemical biosensing

Electrochemical biosensing is a powerful technique for detecting biomolecules, cells, bacteria and many small molecules in both simple and complex media. A large number of electrochemical biosensors have been developed and widely used in biochemical detection, health and environment monitoring, clinical diagnosis, food-safety control and so on [16–18]. An electrochemical biosensor is basically comprised of three constituents, namely, the biochemical receptor for target recognition, electroactive probe for generating target concentration-associated electrical signals and substrate electrode for recording the signals.

According to the receptor, electrochemical biosensors can be classified into various categories, such as enzyme-based biosensors, immunosensors, aptamer-based biosensors and peptide-based biosensors (Fig. 6a) [16]. Enzyme-based biosensors are the most widely utilized electrochemical biosensors for detecting small molecules, including reactive oxygen species, glucose, lactate, uric acid, ascorbic acid, cholesterol and drugs [83]. In an enzyme-based biosensor, the target-specific enzyme is physically or chemically immobilized on the electrode surface to catalyze the oxidation of target molecule via a certain redox mediator, such as ferricyanide, ferrocene, transition metal or metal complex. This process will generate a current signal in direct proportional to the concentration of target analyte, thus accomplishing the quantitative analysis. Thanks to their simple fabrication, low cost, high sensitivity and high selectivity, enzyme-based biosensors have been extensively integrated into portable, wearable and implantable devices for point-of-care testing of glucose and metabolites. A brilliant example is glucose electrochemical sensor, the most commonly used enzyme-based biosensor [84], in which glucose is first oxidized by a redox mediator (e.g., the osmium-derivatized polymer) via the catalysis by glucose oxidase (GOx). The reduced mediator is subsequently oxidized at the electrode surface, producing current with the magnitude directly proportional to the glucose concentration. The

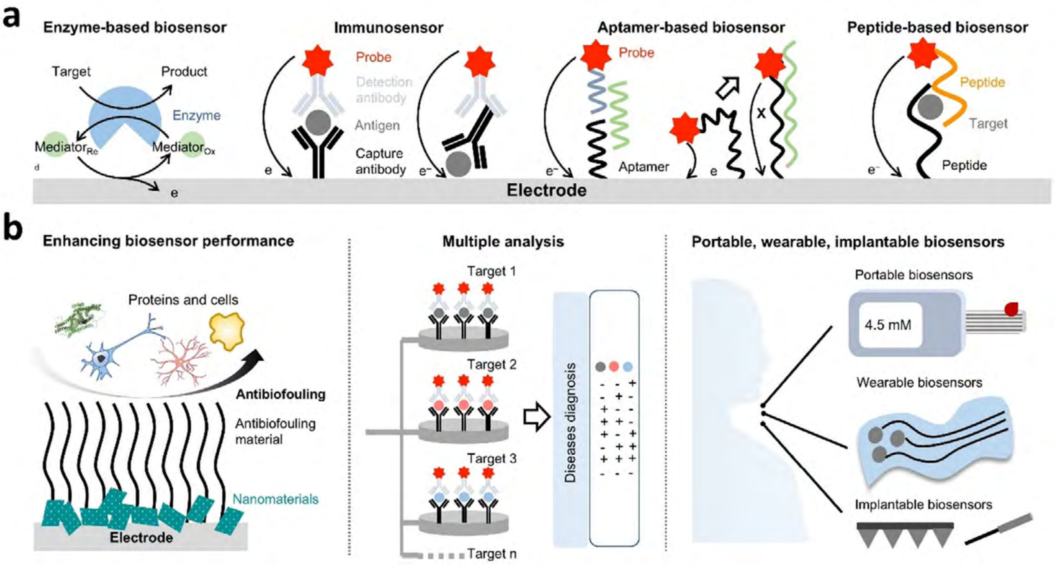

Fig. 6. Hierarchical design principles of biosensing platforms. (a) Sensing mechanisms of enzyme-based biosensor, immunosensor, aptamer-based biosensor and peptide-based biosensor. (b) The present development of electrochemical biosensors on enhancing biosensor performance, multiple analysis and portable, wearable, implantable biosensors. Reproduced with permission of Refs. [16] and [88].

commercial glucose electrochemical sensors, such as fingertip blood glucose meter and the Abbott FreeStyle Libre device, have been successfully applied in the monitoring of glucose in blood and interstitial fluid, and significantly renovated diabetes diagnosis and management. Immunosensors, as another group of important electrochemical biosensors, are primarily used for detecting protein biomarkers [85]. In an immunosensor, the antibody or antigen immobilized on the electrode surface captures its target to form a complex. This complex subsequently binds with a detection antibody labeled with an electroactive probe (including enzyme, electroactive molecule and nanomaterial), forming a sandwich-type immune structure. The concentration of target protein biomarker is eventually quantified in terms of the magnitude of electrochemical signal generated by the probe. Despite their relatively complex fabrication, immunosensors can provide excellent selectivity and high sensitivity, which have been widely employed for detecting numerous protein biomarkers of diseases such as cancer, sepsis, cardiovascular disorders and neurodegenerative diseases. The working mechanisms of aptamer- and peptide-based biosensors are similar to that of immunosensors [86]. They enable the quantitative detection of nucleic acids, peptides and bacteria according to the electrochemical signals generated from the sandwich structures. Additionally, aptamer-based biosensors can also work in an alternative mode: the binding of a target RNA to its aptamer induces the formation of double-stranded DNA, which pushes the electroactive probe labeled on aptamer away from the electrode surface, leading to a decrease in the electrochemical signal. Compared with enzyme-based biosensors and immunosensors, aptamer- and peptide-based biosensors have not been widely applied so far.

Notably, the performance of electrochemical biosensors can be significantly enhanced by using advanced signal amplification technologies, including luminescence and photoelectrochemistry. Among these, electrochemiluminescence (ECL) is particularly advantageous [87]. ECL is an electrochemically triggered energy relaxation process, in which luminophores including luminol, quantum dots, ruthenium or iridium complexes undergo ET reactions to form excited states emitting light. The current or potential acts as the excitation source, while the emitted light serves as the readout signal. Compared with amperometric and voltammetric biosensors, ECL biosensors exhibit superior sensitivity and lower background noise, because ECL is free from interferences of biological autofluorescence and scattered light. Moreover, ECL provides excellent spatiotemporal controllability due to the cascade reactions initiated by surface electrochemistry. These advantages make ECL biosensors highly promising for electrochemical analyses that require minimal background interference and ultra-high sensitivity. ECL immunoassays have been successfully commercialized and widely used in clinic for the detection of a variety of protein disease biomarkers.

The present development of electrochemical biosensors is primarily focused on key areas of enhancing the performance of biosensors in real complex biological environments, enabling the simultaneous detection of multiple targets on a single biosensor, and advancing the fabrication of portable, wearable and implantable biosensors for point-of-care applications (Fig. 6b).

Biofouling and biodegradation are major challenges that significantly impact the performance of electrochemical biosensors [88]. Biofouling refers the accumulation of unwanted proteins, cells, biological macromolecules and other organic substances on the electrode surface, which severely decreases electrochemical performance and limits practical applications of electrochemical biosensors. When electrochemical biosensors are exposed to complex biological environments, the natural adsorption and adhesion of proteins and cells will instantly occur on the surface, resulting in the formation of a biofouling layer. The biofouling layer hinders both charge transfer and mass transport, thus causing poor analytical sensitivity, high detection limit, short life-time and high background noise. Various antibiofouling materials including polymers, self-assembled monolayers (SAMs) and porous membranes have been developed to enhance the antibiofouling performance of electrochemical biosensors. Proteins and cells tend to adsorb on and adhere to the surface in some specific configurations through hydrophobic interaction. Polymers and SAMs can bind water molecules and form a dense hydration layer, thereby weakening the hydrophobic interaction and significantly suppressing biofouling effect. Additionally, highly ordered and closely packed nanochannels in porous membranes can serve as physical barriers to prevent the adsorption of large proteins and cells through size exclusion effect, thus avoiding the biofouling [89]. When electrochemical biosensors are used *in vivo*, they will further suffer from immune reactions that induce the formation of a dense fibrous capsule at the surface [90, 91]. The dense fibrous capsule can entirely deactivate the electrochemical biosensors, leading to serious or entire loss of performance. One effective strategy to solve this problem is to reduce the elastic modulus of electrochemical biosensors to match with that of the surrounding biological media [92, 93]. However, biodegradation of enzymes, antigens, antibodies, aptamers and peptides on the electrochemical biosensors remains to be an unavoidable issue, particularly in long-term analysis, which also strongly limits the performance of electrochemical biosensors. In addition to antifouling strategies, incorporating nanomaterials such as graphene, carbon nanotubes, quantum dots, metallic nanoparticles and MXene into electrochemical biosensors can significantly facilitate the electron transfer, thus increasing the sensitivity, decreasing the detection limit and making electrochemical biosensors more effective for various analytical applications.

The detection of multiple analytes on a single electrochemical biosensor is advantageous over traditional single target detection, offering more comprehensive and reliable test result, shorter analysis time, reduced cost and minimized false positive or negative [94]. Multiplex analysis is particularly beneficial for the simultaneous quantification of various proteins, nucleic acids and other biomarkers in a single step using minimal sample volume, which is very helpful to rapid and precise diseases diagnosis. One of highly effective approaches of achieving multiplex detection is to use electrode arrays. Different materials, including carbon, graphene, gold, platinum and indium tin oxide, have been successfully modified on both rigid and flexible substrates to fabricate electrode arrays using advanced fabrication techniques such as screen printing, 3D printing, magnetron sputtering, electron-beam evaporation and etching. The size, number, shape, and spatial arrangement of electrodes within each array can be precisely controlled. However, the increased complexity of electrode structure may introduce difficulties in reagent delivery, receptor immobilization, sandwich assay formation and signal detection. To address these issues, the electrode array is often combined with miniaturized microfluidic chip and multi-channel electrochemical workstation to realize fully automated biosensor fabrication and detection.

Portable, wearable and implantable electrochemical biosensors have emerged as powerful tools for rapid and real-time analysis of protein biomarkers and disease-related small molecules in both in vitro (blood, serum, sweat, tear and other biofluids) and *in vivo* (tissues and organs) environments, thereby expanding the practical applications of electrochemical biosensors. Blood glucose meters are the most widely used portable biosensors for monitoring blood glucose level. Glucose meter contains a disposable test strip for electrochemical detection and a handheld reader for data output. The disposable test strip is fabricated through screen-printing conductive carbon ink on plastic substrates. The sensing layer consisting of GOx and osmium-derivatized polymer is immobilized on the electrode in the test strip. By changing the composition of sensing layer, the glucose meter can also be adapted to detect uric acid, lactic acid and many different metal ions. Paper-based lateral flow immunoassays (LFIAs) are convenient, rapid and cost-effective tools for point-of-care testing of drugs, protein biomarkers, virus and bacteria. In recent year, electrochemical biosensors have been integrated with LIFAs (eLFIAs) to improve their analytical sensitivity, quantitative capability and accuracy [95]. For instance, in the detection of antigens, an electroactive probe-labeled detection antibody and a capture antibody are pre-deposited on the conjugate pad and working electrode (test line of the LFIA), respectively. When a sample containing the target antigen is added dropwise on the sample pad, antigen moves forward and binds with detection antibody and capture antibody to form a sandwich-type immune complex structure on the electrode surface. The antigen is quantified in terms of the current signal generated by the electroactive probe. The portable eLFIAs allow fast and sensitive detection of protein biomarkers, which have been successfully applied in point-of-care testing for cancer and inflammatory biomarkers.

Wearable and implantable electrochemical biosensors are two advanced classes of electrochemical biosensors. Wearable electrochemical biosensors enable continuous, real-time and noninvasive monitoring of small molecules and protein biomarkers in sweat, tear and saliva, offering molecular-level insights into human health. Their effective operation requires conformal contact between the biosensor and the skin or tissue. Fabrics and flexible polymers serve as ideal substrates due to their ability to maintain constant contact with the skin and tissue. Electrodes and electronic components are integrated onto these substrates, allowing continuous electrochemical monitoring. This real-time monitoring provides timely feedback for the management of diseases such as diabetes and hyperuricemia. Implantable electrochemical biosensors, including metal electrodes, microneedle electrodes and carbon/graphene fiber-based microelectrodes, can be implanted into the skin, brain or other organs to monitor small molecules and ions. Among them, microneedle electrode arrays made up of miniaturized needle-like microelectrodes with several hundreds of micrometers in length are particularly interesting [96, 97]. Because of their minimally invasive nature, microneedle electrode arrays can pierce the skin and electrochemically detect glucose, uric acid, drugs and ions in the interstitial fluid. Microneedle electrode arrays have been successfully employed in the development of closed-loop feedback systems for disease management. For example, glucose microneedle electrode arrays enable real-time monitoring of interstitial glucose levels, with data wirelessly transmitted to a user interface for analysis. Then, the information can guide personalized administration of diet, exercise and insulin dosage for diabetes patients. The objective of closed-loop feedback systems is to optimize and advise therapeutic strategies for individual patients to realize personalized management. Moreover, implantable electrochemical biosensors also play a crucial role in brain disease research and diagnosis, which can be implanted in the brain to monitor neurochemical levels and temporal variations across different brain regions with a millisecond resolution [98–100]. Since neurochemicals such as oxygen, glucose, ascorbic acid, neurotransmitters and ions must be maintained at steady-state levels to support neuronal activity, their changes in response to brain diseases often precede detectable changes in genes, proteins and cells. Therefore, implantable electrochemical biosensors have been used to explore biological mechanisms of brain hypoxia, cerebral ischemia, Parkinson's disease and Alzheimer's disease. It is important to note that, apart from high electrochemical performance, implantable electrochemical biosensors must possess high biocompatibility and low biological toxicity due to the severer biofouling in brain. Ensuring long-term stability and functionality in biological environments remains a key challenge in the development of wearable and implantable electrochemical biosensors in future.

In summary, electrochemical biosensors can detect a wide range of biomolecules, cells and bacteria in both simple and complex environments, which offer platforms for health monitoring, clinical analysis, disease diagnosis and therapy. However, the widespread application of electrochemical biosensors still has a long way to go. On one hand, the life-time is greatly limited by the biodegradation and inactivation of biochemical receptors immobilized on the biosensors. They can only work stably for 1–2 weeks, thus the present electrochemical biosensors are not very suitable for electrochemical analysis in a long-time scale. On the other hand, as affected by complex processing procedures, electrochemical biosensors usually display insufficient reproducibility, which not only limits the mass production and wide application, but also decreases the reliability of detection results. How to solve these challenges decides the future development of electrochemical biosensors.

5.2. *Electrochemical microscopic imaging*

The electrically driven excitation mode of electrochemical methods provides excellent temporal control, while their rapid response to subtle system perturbations ensures exceptional sensitivity. When coupled with spatial resolution, these advantages have led to the development of a range of powerful imaging techniques. Notable examples include electrochemiluminescence (ECL) microscopy, which employs optical signal readouts; scanning electrochemical microscopy (SECM) and scanning ion conductance microscopy (SICM), which detect current signals; and electrochemical impedance imaging (ECI), which measures impedance responses. Among these, ECL microscopy, SECM, and SICM are widely applied in the visualization of biological samples and physiological processes due to their high biocompatibility. This section highlights the biomedical applications of these three techniques.

ECL is triggered by electrochemical reactions and read out through optical signals generated at the electrode surface. Its integration with microscopic systems gave rise to ECL microscopy, a technique that has contributed both technical innovations and novel insights into cellular structure, function, and interactions with the surrounding microenvironment. Negative and positive ECL represent two commonly employed paradigms in ECL microscopy. In negative ECL, when an insulating analyte blocks direct contact between free luminophores and the electrode surface, local ECL emission is suppressed, producing images in which the target appears darker than the surrounding area. Owing to its inherent label-free nature, the negative ECL strategy is particularly advantageous for monitoring dynamic changes in cell morphology and molecular activity in living cells. In single-cell imaging based on this principle, the interaction between substrate properties and cellular adhesion can reveal detailed surface information. For instance, Su and colleagues characterized the specific recognition between T-cell receptors and peptide-major histocompatibility complex (peptide-MHC) complexes on the cell membrane (Fig. 7a), as well as the regulatory role of co-stimulatory molecules, providing unique insights into cell–microenvironment interactions [19]. Jiang and coworkers developed an ECL capacitance microscope for label-free imaging of membrane-associated molecules [20]. Moreover, the label-free ECL imaging strategy has successfully visualized individual mitochondria with high clarity [21], demonstrating its promise for subcellular structure imaging.

In contrast, the positive ECL paradigm highlights the analyte as a region of enhanced light emission. For example, biomolecules such as DNA and RNA, which contain amino groups, can act as endogenous co-reactants of the ECL luminophore $[Ru(bpy)_3]^{2+}$, thereby amplifying its luminescence and enabling stratified imaging of cellular structures [104]. Inspired by immunofluorescence imaging, a widely

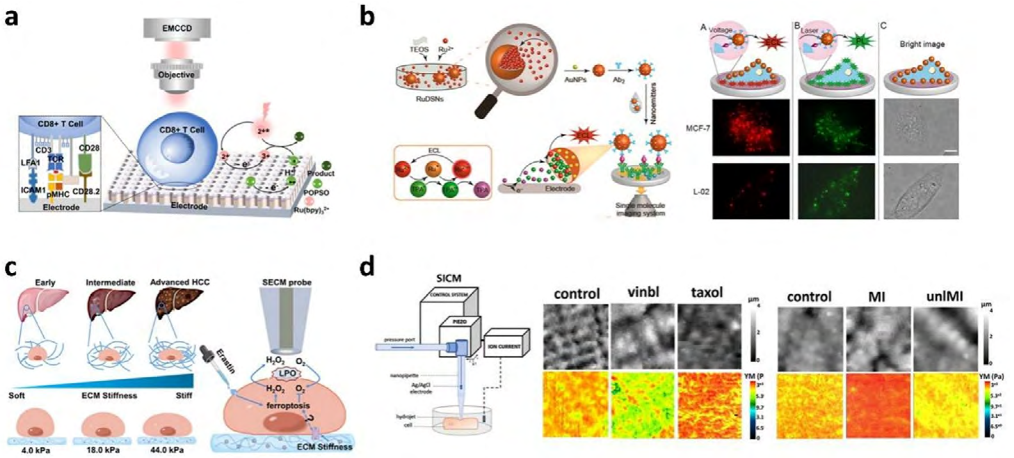

Fig. 7. Electrochemical microscopy modalities for molecular specificity and nanomechanical phenotyping. (a) Evaluation of T-cell receptor (TCR)-antigen specificity in cells using negative ECL microscopy [19]. (b) Visualization of membrane proteins using positive ECL microscopy [101]. (c) Investigation of the effect of extracellular matrix (ECM) stiffness on ferroptosis in hepatocellular carcinoma (HCC) cells using SECM [102]. (d) Measurement of cardiomyocyte transverse Young's modulus regulated by microtubules using mechanoSICM [103]. Reproduced with permission of Refs. [19], [101], [102] and [103].

adopted strategy in cell imaging involves labeling target molecules with ECL luminophores. The key advantage of ECL, namely, its avoidance of external light excitation, eliminates background interference in immunofluorescence. and results in markedly improved sensitivity and signal-to-noise ratios. Nevertheless, a major limitation of this approach lies in the intrinsically weak nature of ECL emission. A well-established strategy to address this challenge involves concentrating luminophores within a single nano-emitter (Fig. 7b). By exploiting nanoscale confinement effects, ECL emission can be localized at the emitter surface, producing significantly stronger signals [101]. This approach has enabled the visualization of specific membrane proteins on individual cells and has shaped the development of numerous subsequent ECL imaging systems.

Beyond visualizing cellular structures and functions, ECL microscopy has also shown promise in disease diagnosis and therapy, offering capabilities that extend beyond simple indication or detection. For instance, ECL has been employed simultaneously as an optical indicator for monitoring cellular pyrolysis and as a light source to activate photosensitizers for generating cytotoxic reactive oxygen species [105]. This dual functionality enables photodynamic therapy (PDT), and integrates both diagnostic and therapeutic functions within a single system. Moreover, substantial progress has been made in ECL-based tissue analysis. Drawing on the surface-confined nature of ECL signals, Jiang and colleagues developed an innovative technique for visualizing extracellular matrix components in tissue without the need for specific labeling [106]. This method has been successfully applied to the rapid identification of tumor tissue in clinical samples. The same group also introduced a label-free enzyme activity imaging strategy based on a luminol ECL system, enabling spatial mapping of multiple enzymes within a single tissue section and revealing aberrant enzyme activation during tumor progression [107]. These advances in ECL microscopy open new directions for disease diagnosis and treatment, and are poised to drive the next stage in the evolution of ECL-based methodologies.

While ECL provides excellent sensitivity in bioanalytical detection, its optical nature imposes a diffraction-limited spatial resolution, which can hinder detailed analysis at the subcellular level. In contrast, SECM and SICM circumvent this limitation through probe-based detection methods that enable high-resolution, label-free mapping of chemical or topographical features on biological samples. SECM, first introduced by Bard and colleagues in 1989, employs an ultramicroelectrode (UME) to detect localized redox reactions or concentration gradients at the interface between the probe and the sample [108]. As the probe scans across the surface, it records faradaic current that reflects electrochemical activity in real time. Through various operational modes, such as feedback or generation–collection, SECM can detect subtle biological signals including pH variations, redox-active molecule release, and enzymatic activity from living cells, achieving micrometer to nanometer spatial resolution. In recent years, SECM has been increasingly applied to investigate disease-related cellular processes. By leveraging the redox interaction between cytochrome c oxidase (COX) and a specific mediator, enzymatic activity was quantified through current changes at a platinum microelectrode, and the apparent heterogeneous rate constant (k^0) was extracted using numerical modeling. This approach, demonstrated by Thind et al., enabled the sensitive and noninvasive detection of COX deficiency in human fibroblasts, a biomarker of mitochondrial dysfunction associated with various neurodegenerative and metabolic disorders [109]. In a series of studies, Zhao and colleagues employed SECM to quantitatively and *in-situ* monitor the early stages of ferroptosis in HuH7 cancer cells, by assessing changes in membrane permeability, respiratory activity, and cellular redox state [110]. Building on this, their subsequent study revealed how extracellular matrix stiffness modulates the susceptibility of hepatocellular carcinoma cells to ferroptosis (Fig. 7c), suggesting a mechanobiological dimension to therapeutic sensitivity [102]. Beyond single-cell analysis, SECM has also shown promise at the tissue level. Lin et al., developed soft, flexible electrochemical probes capable of mapping the spatial distribution of prognostic protein biomarkers in human melanoma and redox-active proteins in mouse heart [111]. Their work highlighted the ability of SECM to provide chemically resolved, minimally invasive imaging in complex biological environments, supporting its potential in translational and clinical applications. Together, these advances underscore the versatility of SECM in probing disease mechanisms, assessing drug responses, and revealing biochemical heterogeneity across cellular and tissue scales.

Complementing the strength of SECM in chemical reactivity mapping, SICM offers a non-contact, high-resolution approach for characterizing surface topography and mechanical properties, particularly suited for soft and dynamic biological samples. First reported in 1989 by Hansma and colleagues, SICM utilizes a nanopipette filled with electrolytes to scan the sample surface, measuring the ion current between electrodes inside and outside the pipette [112, 113]. This current is modulated by the distance between the pipette tip and the sample, enabling nanoscale imaging without physical contact. The technique was further refined by Korchev and coworkers, who adapted SICM for biological applications, making it compatible with live cell imaging in physiological conditions. A key innovation came with the introduction of the hopping mode, which enabled accurate topographical mapping over uneven and highly curved cellular surfaces by implementing a vertical "hop" approach to each measurement point [114]. This advancement significantly enhanced the biological applicability of SICM by imaging delicate cellular structures such as cochlear outer hair cells and hippocampal neurons, enabling the visualization of nanoscale features including stereocilia and membrane protrusions. In another seminal study, Nikolaev et al. combined SICM and fluorescence resonance energy transfer microscopy techniques (FRET) to visualize the redistribution of β2-adrenergic receptors in cardiomyocytes during heart failure, revealing crucial changes in cyclic adenosine monophosphate (cAMP) compartmentalization that affect cardiac signal transduction [115]. Also, in the cardiovascular field, Swiatlowska et al. applied mechanoSICM to measure the transverse Young's modulus of cardiomyocytes (Fig. 7d), uncovering a role for the microtubule cytoskeleton in regulating mechanical stiffness and suggesting mechanotransduction pathways in heart disease [103]. Further advancing its capabilities, high-speed SICM has enabled dynamic visualization of fast biological events. Bednarska et al., captured the rapid assembly of human immunodeficiency virus (HIV)-like particles on the surface of living cells, providing a powerful tool to investigate viral budding mechanisms in real-time [116]. Similarly, Takahashi and collaborators developed the automation region of interest (AR)-mode SICM to monitor transient structural changes in hippocampal neurons, offering nanoscale insights into neuronal plasticity and signaling [117]. These applications collectively illustrate the unique advantages of SICM in the non-invasive, high-resolution study of cellular morphology, mechanical behavior, and dynamic membrane events.

Taken together, SECM and SICM represent two complementary modalities in electrochemical imaging, each addressing different but synergistic dimensions of biological interrogation. SECM is ideally suited for mapping redox chemistry and cellular metabolic activity, while SICM excels at capturing structural and mechanical information from delicate biological surfaces. When used in combination or alongside other analytical modalities such as fluorescence microscopy, electrochemical impedance, or even ECL microscopy, these techniques offer a multidimensional perspective that is highly valuable for modern diagnostics, disease modeling, and personalized therapeutic research.

5.3. Electrochemiluminescence detection

5.3.1. Electrochemiluminescence biosensing

ECL is a key branch of electrochemical (EC) technology, where electrogenerated radical reactions near the electrode convert the EC signals into light emission [118, 119]. ECL integrates the exceptional sensitivity of chemiluminescence (CL) with the high spatiotemporal controllability of EC methods, enabling localized signal activation/deactivation with minimal background interference while eliminating the need for external excitation light source. Hence, ECL techniques holds assay versatility, intrinsic signal amplification, and advanced detection mode, resulting in its high performance in rapid and precise disease diagnostics [120, 121]. Since its first systematic investigations by Hercules and Bard in the 1960s, ECL has evolved into a highly sensitive biosensing technique for detecting disease biomarkers including nucleic acids, proteins and metabolites, etc. in various body fluids at remarkably low concentrations (pmol·L^{-1} to fmol·L^{-1} levels) [22–24]. ECL biosensing detection relies on the quantitative correlation between ECL signal and analyte concentration, utilizing bioactive molecules as recognition elements and ECL reagents as signal substances to convert biochemical interactions into quantifiable luminescent signals. According to detection principles, ECL biosensing strategies mainly include ECL immunoassay, nucleic acid biosensing, and cytosensing assays.

ECL Immunoassay. The ECL immunoassay operates on similar principles to conventional immunoassays but with enhanced sensitivity. In these systems, antigens or antibodies conjugated with ECL luminophores are immobilized on an electrode surface, and the target-involved specific recognition reactions modulate the ECL signal, enabling ultrasensitive quantification of biomarkers. Various ECL immunosensing systems, including label-free, sandwich-like (indirect detection), and competitive immunosensing, have been applied to detecting disease-related biomolecules [122, 123]. As a subclass of these biomolecules, protein biomarkers continue to be pivotal target analytes in ECL immunoassay, especially in sandwich-like systems [123, 124]. Xu et al. designed a biomimetic sandwich-like immunosensor targeting serum amyloid A (SAA), a biomarker of COVID-19 [125]. To overcome aggregation-induced emission quenching, they encapsulated the ECL-active molecule TBAPy in liposomes (TBAPy-Lips), enhancing the stability and sensitivity of the ECL system. TBAPy-Lips labeled with secondary antibodies served as a biomimetic ECL probe within closed-loop system that combined a gold nanocrystal film-modified electrode and thiolated-antibodies. This system exhibited excellent specificity and sensitivity, achieving a LOD of 0.188 pg·mL^{-1} for SAA and stable performance with an RSD of 1.24%. Thus, this sandwich-like immunosensor provided a stable, sensitive platform for protein biomarker detection. ECL label-free sensing strategy requires only one unlabeled antibody in the electrode system and has recently garnered significant attention. This approach relies on the direct and selective binding of specific antibodies to antigens (disease biomarkers), leading to changes in the physical parameters of ECL without a secondary antibody. Chen and his coworkers proposed a label-free ECL immunosensing platform utilizing two-in-one HER-AuNCs ECL probes [126], which integrate the immunological recognition capabilities of HER with the ECL performance of AuNCs for the clinical evaluation of the HER2 extracellular domain in breast cancer patients. Coupled with the low potential and high ECL intensity of the HER-AuNCs/DIPEA-OH system, this ECL biosensing method enabled the direct immunoassay of HER2 with a LOD of 11 pg·mL^{-1}. Moreover, it classified individuals with different low-expression statuses of HER2, providing precise guidance for antibody-drug conjugate therapy decisions in cancer patients. Competitive ECL immunosensing employs a binding competition mechanism between labeled probes and unlabeled target analytes for limited antibody recognition sites, causing the decrease of ECL signal as the concentration of target antigens increases for quantitative detection [120]. Dong et al. designed a competitive immunosensing strategy based on a dual quenching mechanism of ECL energy/electron transfer between POM-ZrO_2 and PANI@AuNPs. PANI@AuNPs were used as an energy acceptor to absorb the ECL emission of POM-ZrO_2, and their suitable energy levels provided the necessary conditions for electron transfer, thereby quenching the ECL signal of POM-ZrO_2. The dual-mechanism quenching method showed excellent analytical performance in 17β-estradiol immunoassay. This immunosensing strategy provided a novel detection model for biomarkers precise detection [127]. Moreover, Cai et al. recently developed a $Gd(OH)_3/Eu(OH)_3@TiO_2$ co-reaction competitive ECL sensing platform, enabling precise detection of progesterone in complex samples and unlocking new possibilities for its impactful application in food and environmental analysis [128].

ECL Nucleic Acid Biosensing. This biosensing has emerged as a powerful analytical strategy that utilizes DNA/RNA as biorecognition elements for sensitive detection of nucleic acid sequences, disease biomarkers, and pathogen genes. Its core principle is based on the inherent recognition ability of nucleic acids (e.g., DNA/RNA hybridization, aptamer-target binding) and self-assembly capability to convert biological signals generated on the electrode surface into detectable ECL signals for target-specific analysis. With its versatility and portability, this technology is vital in precision medicine (e.g., detecting circulating tumor DNA, microRNA, and gene mutations), infectious disease prevention (e.g., SARS-CoV-2, influenza A virus detection), and other bioanalysis researches. Zhang et al. developed an ECL nucleic acid sensor for detecting the SARS-CoV-2 RdRp gene with a LOD of 0.21 fmol·L^{-1}, utilizing the recognition and cleavage interaction between the RdRp sequence and multifunctional DNA on the Au@Ti nanocomposite surface, which triggered on-off switch of ECL signal. This method provided a universal model for highly sensitive early clinical diagnosis [129]. Subsequently, Zhang et al. designed a potential-selective and encoded ECL nucleic acid sensor by post-engineering CdTe NCs with RNA, further achieving the simultaneous detection of the open reading frame 1ab and the nucleoprotein genes [130]. The approach held promise for fully automated and commercially viable multiplex gene testing. Similarly, Li et al. built an integrated tri-double resolution strategy based on binding-induced DNA strand displacement, successfully analyzing different m6A-RNAs simultaneously [131]. Moreover, ECL nucleic acid biosensing also makes progress through synergistic innovation in nanomaterials, signal amplification, and microfluidics, solidifying its role as a key technology for sensitive, rapid, and cost-effective diagnostics in clinical and point-of-care testing. This chapter will not elaborate further.

ECL Cytosensing Assays. ECL cytosensing detects cellular physiology, metabolism, morphology and molecular distribution by interacting with target cells via specific probes, markers, or portable devices, analyzing them based on ECL emission feedback. According to assay patterns, ECL cytosensors are classified into cellular measurement and cell imaging. This section mainly emphasizes representative studies and recent advances in cellular measurement [132]. Circulating tumor cells (CTCs) play a crucial role in cancer metastasis, making them a research hotspot. ECL cytosensing offers reliable technical support for precise CTC detection and efficient analysis. Li et al. designed a dual-recognition-controlled ECL cytosensor based on aptamer-target binding, enabling the detection and differentiation of specific CTCs among various cancer-like cells in whole blood [133]. By enhancing CTC capture efficiency and analytical precision through the dual-molecule recognition mode, this strategy promoted the versatility and adaptability of direct detection-based ECL cytosensing in complex bio-matrices. Recently, Ding's team developed a high-efficiency antifouling interface strategy, enabling dynamic trace detection of CTCs with a detection limit of 3 cells per milliliter, offering a new reference for a stability and reproducibility analysis in clinical CTC screening [134]. Besides, extracellular and intracellular measurements are also an important topic in ECL cytosensing analysis. For example, Huang's group developed a confined ECL microarray chip using microfluidic technology to trap individual cells in micropores and enable high-throughput, *in-situ* detection of single-cell dopamine without co-reactant, providing a general cytosensing strategy for measuring single-cell secretions [135]. Jiang's group developed a BPE-ECL platform that employed SWCNTs labeled with anti-KDM1/LSD1 antibodies to enter the cell nucleus [136]. After binding to antigens, ECL from L012 enabled the wireless detection of intracellular proteins. This method required direct electrode-cell contact, reducing the applied voltage, and provided a high-sensitivity, low-background approach for intracellular analysis and advanced the development of single-cell electrochemistry.

5.3.2. Electrochemiluminescence amplification strategies

Although ECL detection offers exceptional sensitivity, its clinical application faces challenges due to low abundance of biomarkers in biological samples. The rational integration of signal amplification strategies can overcome this limitation, expand the detection range, and serve as a major driving force for innovation in ECL biosensing. Currently, two commonly amplification strategies have been successfully applied in ECL system, including the physical/chemical amplification of nanomaterials and the DNA-mediated biochemical amplification strategies (Fig. 8) [137–140].

DNA-mediated ECL signal amplification strategies employ various DNA amplification techniques, such as hybridizationchain reaction (HCR), rolling circle amplification (RCA), and DNA walkers etc., to rapidly amplify target nucleic acids within a short period. This amplification increases the number of detectable biomolecules, thereby enhancing the sensitivity of ECL biosensing systems. Nanomaterials, with their excellent conductivity, electrocatalytic activity etc., serve as signal modulators and synergistic reaction catalysts in ECL systems. They not only act as substrates to accommodate more luminophores and biorecognition elements but also facilitate electron transfer during the co-reactant catalysis process, thereby improving photon yield [141]. As a non-invasive and highly specific disease biomarker, exosomes are key mediators for disease surveillance and personalized medicine. Addressing the challenges in exosome precise analysis, Dong's group designed a DNA bio-barcode and HCR-mediated ECL dual amplification strategy for ultrasensitive exosome detection, achieving a LOD of 5.01 particles/μL. Two Apt/NP probes enabled specific recognition, DNA barcode release, and HCR-triggered ECL signal enhancement, allowing precise differentiation of non-target exosomes and demonstrating its potential application in exosome-related clinical diagnostics [137]. Zhang et al. developed a DNAzyme Walker on a functionalized electrode with a cyclic DNA shielding structure. Upon target RNA binding, an enzymatic cleavage

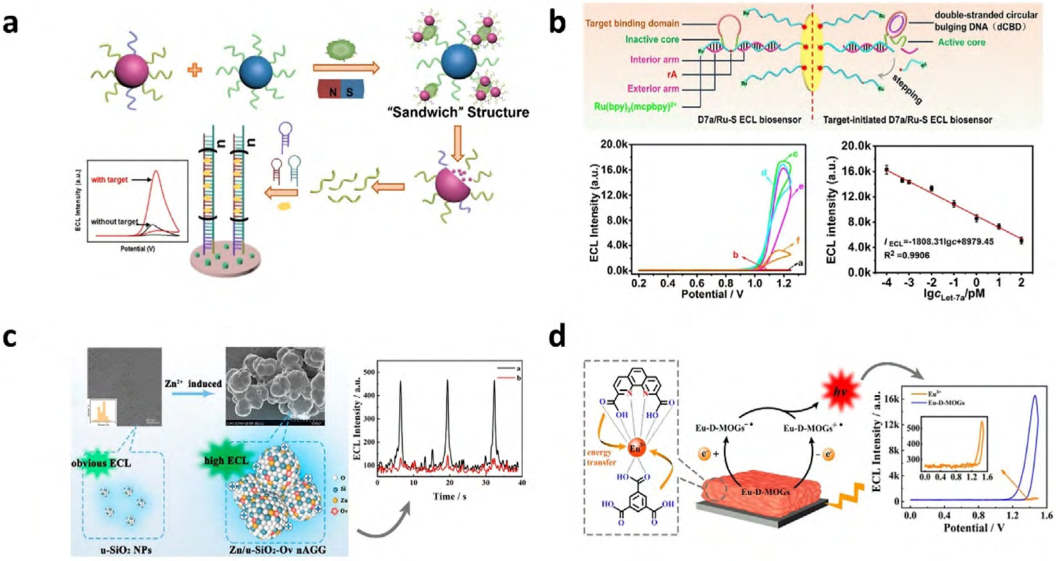

Fig. 8. Different amplification strategies based on nucleic acid and nanomaterials for enhanced ECL detection. (a) Illustration of a sensitive ECL biosensor with HCR for exosome analysis. (b) The DNAzyme Walker-based biosensor for RNA determination. (c) Scheme of the ECL-enhanced biosensing based on Zn/u-SiO$_2$-Ov nAGGs signal amplification for HIV-DNA detection. (d) Reaction mechanism of the ECL-enhanced sensing platform based on the Eu-S-MOGs ECL system for miR-221 detection. Reproduced with permission of Refs. [137–140].

cycle was triggered, releasing Ru(II)-labeled DNA fragments and significantly reducing the ECL signal. This method enabled highly specific RNA detection down to 51.4 amol·L^{-1} with excellent stability and reproducibility. This DNA-based amplification strategy further enhanced the capability of ECL sensing analysis tools for rapid and ultrasensitive detection [140].

Similarly, nanomaterial-based amplification strategies have achieved comparable detection (50.48 amol·L^{-1}). Duan et al. explored the ECL performance of u-SiO$_2$ NPs and significantly enhanced their efficiency through size modulation and Zn^{2+}-induced surface state optimization. They further developed an ECL multi-signal amplification strategy based on u-SiO$_2$ NPs, enabling ultrasensitive HIV-DNA detection (LOD: 50.48 amol·L^{-1}) [138]. This study not only elucidated the ECL mechanism of ultra-small nanomaterials but also provided a new technological pathway and potential applications for ECL biosensing. Following this trend, Zhao et al. introduced an innovative dual-ligand Eu-D-MOGs-enhanced ECL system. By optimizing ligand coordination, Eu-D-MOGs effectively improved charge transfer and enhanced the antenna effect, thereby increasing ECL efficiency. This high-performance ECL nanoemitter enabled the detection of miR-221 at an ultralow concentration of 5.12 amol·L^{-1}. Notably, this study advanced the design of coreactant-free ECL emitters and demonstrated robust performance in real biosample detection [139]. These continuous innovations in ECL amplification strategies not only overcome the limitation of low biomarker abundance but also drive advancements in ECL biosensing and its applications in precision medicine.

5.3.3. *Electrochemiluminescence single-molecule measurement*

Despite the outstanding sensitivity of ECL sensing analysis and the incorporation of various signal amplification strategies to expand its detection capabilities, its detection mode remains constrained by statistical limitations (signal-to-noise ratio constraints, Poisson statistical errors, ensemble averaging effects, etc.). To this end, researchers are striving to push the limits of detection sensitivity and advance ECL single-molecule analysis (ECLSM), providing a powerful tool for studying biomolecular interactions, detecting ultra-trace biomarkers and enabling digital quantitative analysis. ECLSM analysis includes measurement and imaging. ECL single-molecule imaging integrates optical microscopy techniques to resolve the ECL emission characteristics of individual molecules from a spatial perspective, enabling high-resolution imaging (see Section 7.4). In contrast, ECLSM measurement primarily relies on luminescence intensity analysis, utilizing statistical evaluation of single-molecule ECL events to achieve ultrasensitive and quantitative detection. In 1995, Collinson et al. through ultramicroelectrode EC induction, successfully detected the ECL signal of single 9,10-diphenylanthracene radical ion reactions in solution for the first time, and revealed its randomness (Poisson distribution).

This breakthrough marked a leap from collective signal measurements to single-molecule resolution, providing unprecedented advantages for ultrasensitive analysis of individual targets [142]. Since then, efforts to refine ECL single-molecule detection have focused on expanding its application from fundamental proof-of-concept studies to practical analytical challenges. For instance, Liu et al. developed a molecularly imprinted ECL sensor that employed a water-soluble luminol derivative encapsulated within liposomes, which, upon a light-triggered click reaction, released multiple probes to amplify the ECL signal and achieved single-molecule detection of the metabolite AMT at single-molecule level. This represented not only significant advancement in ECLSM measurement from generic luminescent molecule detection to target food safety applications but also highlighted its potential in clinical diagnostics [28]. Recently, Kim et al. demonstrated the power of ECLSM measurement in biomolecular discrimination by developing a proline-selective ECL assay to distinguish A1 and A2 β-casein variants. This method capitalized on the unique ECL properties of proline to resolve a single amino acid substitution, a structural variation that significantly impacted digestion and potential health effect [143]. By directly detecting protein variants without the need for antibodies or complex pretreatment, this represented an important breakthrough in ECLSM measurement for personalized nutrition analysis, advancing the precision of biomolecular differentiation and health assessment.

5.4. Membrane potential and neurotransmitter analysis

The membrane potential is generated by the transmembrane ion concentration gradient and selective permeability of the cell membrane. At rest, this potential (negative inside relative to outside) is primarily maintained by the outward flow of K^+ ions. Action potentials, initiated by the rapid influx of Na^+ ions, are coupled with Ca^{2+} influx, which serves as a critical step in triggering neurotransmitter release. Upon binding to receptors, neurotransmitters activate ion channels and thereby alter the membrane potential, establishing a closed-loop "electrical-chemical-electrical" signaling cascade. Electroanalytical techniques (e.g., voltammetry and potentiometry) enable real-time monitoring of dynamic changes in membrane potential and neurotransmitter activity by recording potential or current signals, providing critical insights into neurochemical-electrophysiological coupling mechanisms.

5.4.1. Membrane potential analysis

The classical approaches for measuring cellular membrane potential primarily rely on two methodologies: (1) direct recording via high-resistance seals between microelectrodes and cell membranes (patch clamp technique), and (2) intracellular microelectrode insertion to measure transmembrane potential differences. Besides single-cell modes, microelectrodes enable high spatiotemporal resolution and high-throughput recording of membrane potential-related neuronal electrical activities, such as action potential spikes, local field potentials (LFPs) and electrocorticography. Zhao et al. [25] synthesized multiple specific ionophores for Na^+, K^+, Ca^{2+} and pH determination, and further developed an electrochemophysiological microarray (ECPM) through the integration of multiple ion-selective electrodes. This system achieved real-time mapping, and simultaneous quantification of chemical and LFPs signals in freely moving rat brains (Fig. 9a).

Implantable tools inevitably cause immune response and recording drift caused by the mechanical, and structural mismatch between these devices and brain tissues, thereby limiting the long-term stable recording of behaving animals. Miniaturized flexible

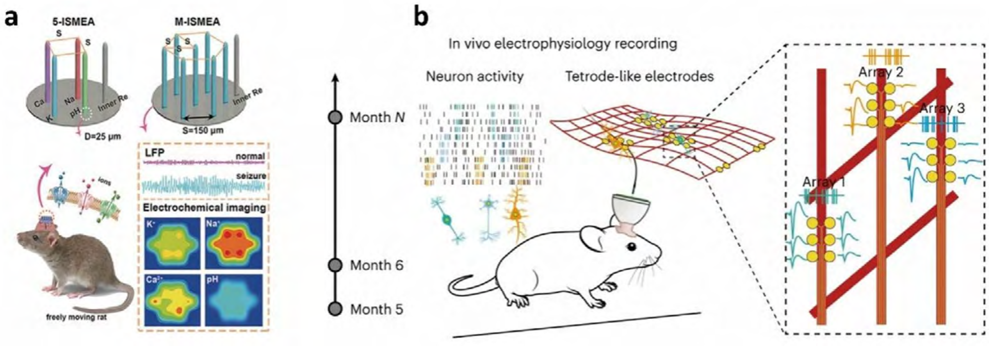

Fig. 9. Scalable hardware interfaces for multiplexed chronic physiological interrogation. (a) Schematic of two types of the ECPM: a 5-channel and 8-channel ion-selective microelectrode array (ISMEA) systems designed for simultaneously quantification of multiple ions. [25] (b) An open mesh structure electronic for year-long implantation and single-unit action potential recording [144]. Reproduced with permission of Refs. [25] and [144].

electronics can finely address this challenge by mimicking tissue-like structural and mechanical compatibilities. Zhao et al. [144] has introduced a method to precisely implant electrodes with an open, unfolded mesh structure across multiple brain regions in the mouse. The open mesh structure formed a stable interwoven structure with the neural network, preventing probe drifting and showing no immune response. This allowed single-unit action potentials recording from the same neurons of behaving mice during the year-long implantation (Fig. 9b).

Beyond the utilization of microelectrodes to record signals associated with membrane potential variations, memristors with their dynamic resistance modulation and ion migration characteristics, enable the physical emulation of biological synaptic functionalities, including neuronal membrane potentials. Xiong et al. [145] fabricated a polyimidazolium brush-confined fluidic channel and successfully emulated behaviors of chemical synapses for the first time, such as short-term plasticity and neurochemical-electrical signal transduction. Further, Xie et al. [146] reported an ion-shuttling memristor with both neuromorphic functions and K^+ selectivity by incorporating dissolved K^+-selective ionophores and stabilizers in dichloroethane liquid membrane, mimicking ion selectivity-dependent neural functions, such as resting potential.

5.4.2. Neurotransmitter analysis

Amperometry enables precise quantification of electroactive substances by detecting Faradaic currents generated from redox reactions at the working electrode surface under a constant potential. Leveraging single-cell amperometry (SCA) pioneered by Wightman and intracellular vesicle impact electrochemical cytometry (IVIEC) developed by Ewing and colleagues, micro/nano-electrodes with high temporal and spatial resolution have propelled neurotransmitter detection to single-cell and single-vesicle levels (Fig. 10a). These advancements provide quantitative and dynamic insights into vesicular neurotransmitter storage, exocytotic release, and fusion pore kinetics [26]. Notably, Yue et al. [147] employed these technologies to investigate sex-specific differences in neurotransmitter dynamics, and found that males exhibited longer durations and a more significant release during individual catecholamine exocytosis events,

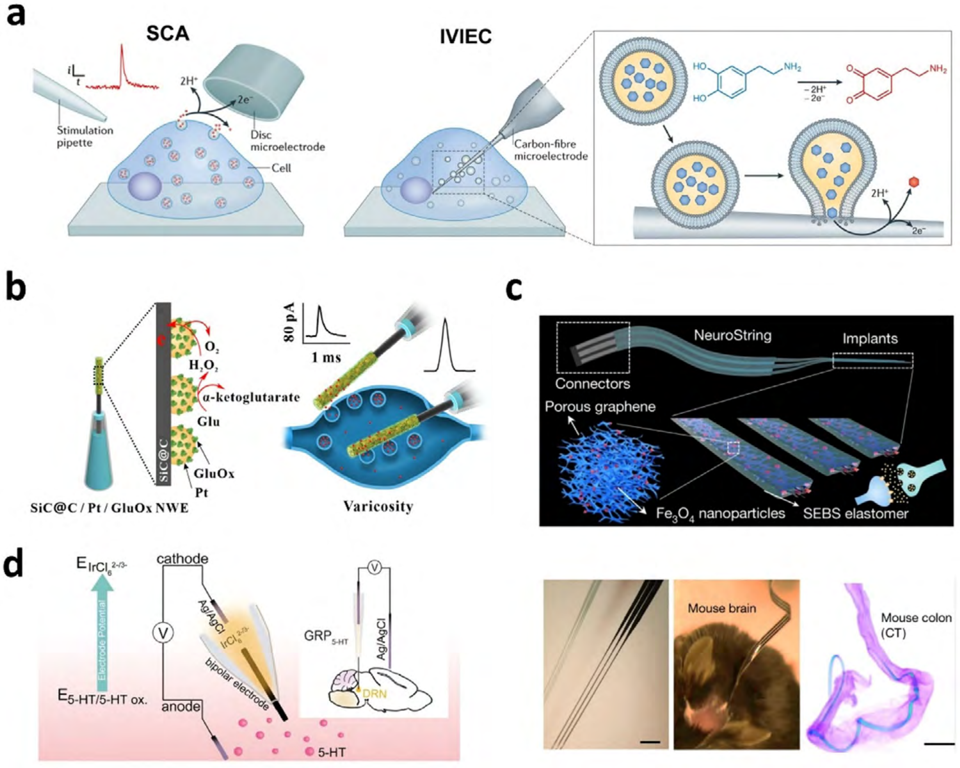

Fig. 10. Interfacial biosensing platforms resolving neurotransmitter dynamics across biological scales. (a) Quantitative analysis of vesicular transmitter storage and exocytotic release with SCA and IVIEC [149]. (b) Amperometric monitoring of vesicular Glu exocytotic release or intravesicular content by the Glu nanosensors [148]. (c) Schematic of the soft implant for neurotransmitters sensing in the brain and gut [150]. (d) Schematic illustration of $GRP_{5\text{-}HT}$ *sensor in the galvanic cell configuration and in vivo monitoring of 5-HT dynamics in the DRN of a living guinea pig [151]. Reproduced with permission of Refs. [148–151].*

revealing the sex dimorphism in single-vesicle exocytosis. While conventional amperometry mainly relies on the intrinsic redox activity of target analytes, it precludes the detection of non-electroactive neurotransmitters. To overcome this constraint, Yang et al. [148] introduced enzyme-functionalized nanosensors, where glutamate oxidase selectively catalyzes the conversion of glutamate (Glu) neurotransmitters to electroactive H_2O_2. The developed Glu nanosensors provided the first direct evidence of sub-quantal Glu release from hippocampal neuronal vesicles (Fig. 10b). Furthermore, they revealed that *β*-amyloid oligomers (Aβ) amplify intravesicular Glu storage and potentiate stimulation-induced release, establishing a quantitative paradigm for studying Glu excitotoxicity in neurodegenerative pathologies [152].

Fast-scan cyclic voltammetry (FSCV) is also a widely used technique for measuring sub-second concentration changes of neurotransmitters under high scan rates (>100 $V\cdot s^{-1}$), which provides fingerprint cyclic voltammograms that identify neurotransmitters at the level of single cells, tissues and *in vivo* [153]. Shin et al. [154] implanted carbon fiber microelectrodes into specific brain regions of adult *Drosophila* and achieved real-time monitoring of dopamine (DA) release during sugar feeding with FSCV technique. To achieve selective and simultaneous measurement of multiple neurochemicals *in vivo*, Xue et al. [155] combined FSCV with deep learning algorithms to simultaneously monitor the dynamic changes of DA, ascorbate (AA), and ions in the living rat brain. Their findings reveal the interplay of neurochemicals during spreading depression. However, most existing sensors are often rigid and brittle, which lead to early device failure or severe inflammatory responses when implanted in soft tissues. To solve this problem, Li et al. [150] developed a novel, highly flexible, stretchable, and biocompatible NeuroString sensor based on laser-induced graphene. By integrating FSCV, they successfully achieved real-time monitoring of DA release in the brains of mice and serotonin dynamics in the actively moving gastrointestinal tract (Fig. 10c).

Differential Pulse Voltammetry (DPV) with small amplitude and short pulses superimposed on a linear ramp, effectively reduces the background current and offers a Faradaic current that is mostly free of capacitive current. To selectively enrich target molecules and accelerate electron transfer rates, strategies involving the functional modification of electrode surfaces using polymers, DNA-based aptamers, covalent organic framework and metal-organic framework (MOF) have been proposed [156–158]. For instance, Wang et al. [157] decorated the conductive MOF Ni_3HHTP_2 on the surface of carbon fiber microelectrodes coated with gold nanoleaves, achieving a detection sensitivity of 1 $nmol\cdot L^{-1}$ for DA. This realized real-time monitoring of DA levels in the brains of live normal mice and those with a Parkinson's disease model.

Among electroanalytical technologies, organic electrochemical transistors (OECTs) stand out for neurotransmitter detection due to their inherent signal amplification capability and low operating voltage. Li et al. [159] proposed a novel strategy based on fast-scanning potential gating (FSP) to enhance the performance of OECTs. This approach integrated the selectivity of fast-scan cyclic voltammetry (FSCV) with the high sensitivity of OECTs, and leveraging transconductance as the sensing parameter, significantly improved the sensitivity, detection limit (5 $nmol\cdot L^{-1}$), reproducibility and stability of the sensor. Specifically, the OECTs demonstrated the real-time monitoring of both the basal levels of DA and its release induced by electrical stimulation in the living rat brain.

Although amperometry or voltammetry fulfills critical criteria for neurotransmitter detection, their dependence on electrolytic cell principles inevitably introduces electrochemical artifacts, such as polarization effects and interfacial double-layer perturbations. To circumvent these limitations, Wu et al. [151] pioneered a galvanic redox potentiometry (GRP) strategy, merging the current-free nature of potentiometric sensing with the spontaneous redox dynamics of galvanic cells. This innovation establishes a self-powered galvanic system that drives analyte-specific redox reactions without external polarization, enabling precise quantification while mitigating electrochemical interference. Based on this methodology, a self-powered single-electrode serotonin ($GRP_{5\text{-}HT}$) sensor has been fabricated and implanted into the dorsal raphe nucleus (DRN) of guinea pigs. The $GRP_{5\text{-}HT}$ sensor maintained remarkable stability (<3% signal variation) during continuous 2-hour monitoring of endogenous 5-HT release (Fig. 10d) [160].

The aforementioned electrochemical techniques have distinct advantages in sensitivity, spatiotemporal resolution and applicability, offering robust and versatile approaches for detecting membrane potential, neurotransmitters, and other biomolecules. Future advancements in integrating miniaturized flexible electrodes with functional nanomaterials will effectively enhance the mechanical compatibility between electrodes and soft tissues for *in vivo* analysis. Concurrently, multi-channel sensor arrays coupled with artificial intelligence algorithms are anticipated to enable synchronized tracking of multiple analytes and decipher complex physiological signaling networks. These technological evolutions hold transformative potential for elucidating mechanisms underlying neurodegenerative disorders, while providing dynamic molecular datasets to advance clinical diagnosis and therapeutic strategies.

5.5. Bioanalysis with flexible electrodes, nanoelectrodes, and nanopore interfaces

Understanding biological processes at the cellular and molecular levels is essential for deciphering the complex interactions that govern life. Recent advances in electrochemical analytical techniques have provided unprecedented insights into biological process from a level of tissue, single cell, to even single molecule. Innovative flexible electrodes, nanoelectrodes, and nanopores have been employed to explore some cutting-edge topics such as mechanotransduction, phagocytosis, and molecule interaction dynamics. Meantime, the electrochemical regulation techniques offer precise and controllable means to modulate these biological processes for their studies. Collectively, these approaches provide fresh perspectives on how cells regulate internal processes and how molecular behavior underpins diverse biological functions.

5.5.1. Flexible electrochemical sensors for cell mechanotransduction

Cell mechanotransduction is a recent hot topic of cellular biological process. The cells are found to be continuously subjected to mechanical forces—such as shear, tensile, and compressive stresses—which are converted into biochemical signals via mechanotransduction [27]. This process is critical for regulating cell function and influencing disease progression in conditions such as osteoarthritis, neurodegeneration and atherosclerosis. Emerging stretchable electrochemical sensors can seamlessly comply with the mechanical deformation of cells and simultaneously monitor biochemical signals in real time, have made significant breakthroughs in exploring mechanotransduction process from tissues down to single-cell levels.

For the tissues, the stretchable sensors were integrated into cartilage and skeletal muscle chips, enabling real-time monitoring of biochemical signals released from engineered tissues. Recognizing the critical role of redox signaling in skeletal muscle tissue, Li et al. [161] fabricated dual flexible fiber sensors by twisting CNTs into helical fiber bundles, and integrating H_2O_2 and NO sensing components. These soft fiber sensors enabled simultaneous monitoring of H_2O_2 and NO releases from engineered skeletal muscle under various exercise-mimicking stretches. Quantitative results indicated that appropriate warm-up activities before high-intensity exercise could enhance tissue adaptation via down-regulation of H_2O_2 and up-regulation of NO production (Fig. 11a). Additionally, Qin et al. [162] developed a cartilage-on-a-chip device with real-time NO sensing capabilities by integrating a 3D Au nanotube based-flexible sensor, and revealed a synergistic effect between mechanical compression and the inflammatory mediator IL-1β on NO release from cartilage tissue.

Stretchable sensors have also been successfully applied to single cell to study exocytosis—a fundamental process by which neurons release neurotransmitters, exemplifying mechanosensitive events. To investigate how mechanical forces regulate vesicular release at the single-cell level, Yan et al. [163] developed a micrometer-scale stretchable electrode using

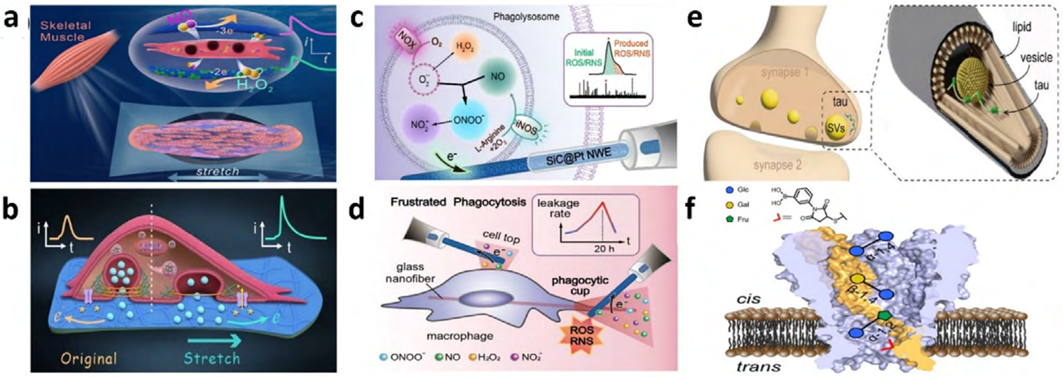

Fig. 11. Real-time quantitative monitoring of dynamic biological processes across scales. (a) Schematic diagram of dual flexible fiber sensors for monitoring of redox signaling molecules in exercise-mimicking engineered skeletal muscle [161]. (b) Schematic diagram of stretchable microelectrodes for real-time quantifying of strain-induced catecholamine release from single vesicles [163]. (c) Schematic diagram of quantitative monitoring of initial and freshly produced ROS/RNS released by individual phagolysosomes with a Pt-coated nanowire electrode (SiC@Pt NWE) [164]. (d) Schematic diagram describing the use of a SiC@Pt NWE for monitoring the released ROS/RNS fluxes during frustrated phagocytosis of a glass nanofiber by a macrophage [165]. (e) Schematic diagram of electrochemically monitoring single vesicle dynamics induced by lipid-tau interactions with a synapse-mimicking nanopipette [29]. (f) Schematic diagram of discriminating disaccharide isomers with different glycosidic linkages with an PBA-modified MspA nanopore [166]. Reproduced with permission of Refs. [29], [161], and [163–166].

microfabricated functionalized PEDOT conductive ink (Fig. 11b). The microelectrode was stretched to apply mechanical strain to a single adrenal chromaffin cell while concurrently monitoring strain-induced vesicular exocytosis. The results demonstrated that mechanical strain rapidly activates the Piezo1 ion channel in chromaffin cells, thereby triggering vesicular exocytosis and increasing catecholamine release.

5.5.2. Nanoelectrodes for phagocytosis process and immune homeostasis monitoring

Another cutting-edge topic on the regulatory functions at single or sub-cellular level is about immune homeostasis. In this process, the macrophages play a crucial role in immune protection by eliminating pathogens, cellular debris, and damaged cells. Upon encountering pathogens, macrophages extend pseudopodia to capture and internalize invaders into vacuoles called phagosomes. These phagosomes subsequently fuse with lysosomes to form phagolysosomes, where enzyme systemsare activated to generate reactive oxygen and nitrogen species (ROS/RNS) for digesting biomolecular entities [28]. Precise regulation of immune homeostasis during phagocytosis is essential for both effective pathogen clearance and macrophage self-protection. Notably, Pt-black nanoelectrochemical sensors—with their excellent spatial, kinetic, and chemical resolution—can quantitatively differentiate ROS/RNS levels, enabling the monitoring of immune homeostatic processes during phagocytosis.

To further elucidate the homeostatic mechanisms of phagolysosomes, Pt nanoparticle-coated nanowire electrodes have been used in conjunction with intracellular vesicle impact electrochemical cytometry (IVIEC) to quantitatively analyze ROS/RNS levels within individual phagolysosomes (Fig. 11c) [164]. Interestingly, a majority of spikes display a "shoulder" (*i.e.*, current falloff tails that deviate from the expected exponential decay), suggesting that enzyme pools are rapidly reactivated to produce fresh ROS/RNS within milliseconds, thereby maintaining heightened scavenging activity within phagolysosomes [164]. Findings on potential differentiation indicate differences between newly generated and stored ROS/RNS, highlighting a significant shift in enzyme activity as the phagolysosome transitions from an acute inflammatory state to homeostasis. Importantly, nanopipettes with an inner Pt coating are anticipated to enhance the assessment of phagolysosome size and ROS/RNS content [167]. By integrating resistive-pulse sensing and IVIEC technology, these nanopipettes will help establish a correlation between phagolysosomal morphology and immunocidal capacity.

This approach was used to study the phagocytic process of macrophages affected by the foreign substances. Unlike small pathogens, inert fibrous nanomaterials are too elongated and stable for macrophages to fully internalize in a short time frame, which results in "frustrated phagocytosis", Pt nanosensors were used to monitor the intensity and temporal fluctuations of ROS/RNS emissions from individual macrophages during the frustrated phagocytosis of glass nanofibers (Fig. 11d) [165]. The findings revealed significant ROS/RNS release through unsealed phagocytic cups, with flux levels continuing to rise until the glass nanofibers were completely encapsulated [165]. This precise tracking highlights the immune stress response of individual macrophages during prolonged phagocytosis and reveals that persistent dysregulation of immune homeostasis ultimately leads to cellular damage in neighboring cells, contributing to chronic inflammation and lung injury.

5.5.3. Nanopore-based single molecule sensing

Comparing the cells, molecules are more fundamental units of biological process. Understanding the dynamics of their conformational changes is critical for unraveling the mechanisms those drive biological processes from the molecular level. Nanopore-based single-molecule detection has emerged as a powerful technique for assessing both the structural and functional heterogeneity of individual molecules. Unlike conventional electrochemical sensors that rely on the redox properties of analytes, nanopore sensors detect molecules based on their volume or charge. Within the highly confined space of a nanopore, minute conformational changes are transduced into distinct current signals with high temporal and current resolution, enabling high-throughput, label-free characterization of a vast number of molecules and opening new avenues for studying diverse molecular interactions.

Some notable application involves examining the interaction between proteins and synaptic vesicles (SVs) and two kinds of proteins. Chen et al. [29] confined a model vesicle within a lipid-modified nanopipette to mimic the synaptic environment. They discovered that phosphorylated tau proteins exhibit a higher binding affinity for SVs, which may impede vesicle mobility and consequently affect neurotransmitter release (Fig. 11e). The ligand-receptor-anchored nanopores were used to track dynamic multivalent interactions between soluble angiotensin-converting enzyme 2 (sACE2) and various spike proteins [168]. The consistently robust binding of Omicron spike protein monomers to sACE2 helps explain its enhanced infectivity compared to other variants.

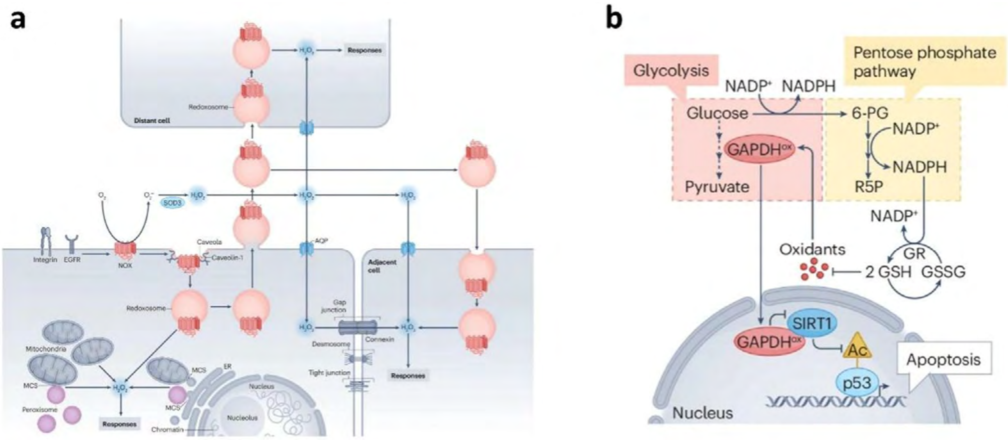

Fig. 12. Electrochemical modulation of substance transformation in biological processes. (a) Schematic illustration of electrochemical regulation within and between cells; (b) an example of metabolic pathways influenced by redox regulation. Reproduced with permission of Ref. [2].

Besides as the targets of research, the biomolecular dynamic interaction can also be used as a tool for detection. The sequencing of polysaccharides is a task traditionally fraught with difficulty due to the complexity of glycosidic linkages. By leveraging the specific interaction between boronic acid and the cis-diol groups in saccharides, Zhang et al. [166] developed a phenylboronic acid (PBA)-modified Mycobacterium smegmatis porin A (MspA) nanopore (Fig. 11f). Assisted by a custom machine learning algorithm, this method has achieved precise discrimination of diverse monosaccharides, offering a groundbreaking approach to polysaccharide sequencing.

6. Electrochemical Modulation of Biological Activities

6.1. Electrochemical modulation of substance transformation in biological processes

Substance transformation—the dynamic conversion of molecules through biochemical reactions—is central to life, driving essential processes such as cellular respiration, ATP synthesis, neurotransmitter signaling, and drug metabolism (Fig. 12) [2]. These transformations are governed by electron transfer and energy conversion, often through redox reactions that regulate molecular stability and biological function. For instance, mitochondrial energy production is facilitated by redox cascades in the electron transport chain [169], while synaptic neurotransmission depends on precisely controlled electrochemical gradient [149]. Electrochemical modulation plays a pivotal role in controlling these processes, enabling the fine-tuning of biochemical reactions and energy flow. By modulating electron transfer and redox states, electrochemical techniques can influence the transformation of biomolecules, offering the potential to regulate cellular functions, signal transduction, and metabolic pathways. This capability of electrochemical modulation is transforming our ability to manipulate biological systems, with groundbreaking applications in therapeutic interventions, biosensing, and synthetic biology. By bridging molecular-scale insights with cellular and systemic functions, electrochemical modulation is poised to revolutionize the control and engineering of complex biological processes.

6.1.1. Mechanisms of electrochemical modulation in biochemical reactions

Electrochemical modulation plays a crucial role in biochemical reactions, offering a powerful approach to control and influence chemical processes [170]. This modulation is primarily achieved through the application of electric fields, which can significantly alter the reactivity and pathways of biochemical reactions. Studies on the use of electric fields to modulate molecular activities have highlighted their potential to drive novel catalytic mechanisms and chemical transformations by influencing electron transport and molecular dynamics [171].

A key concept in electrochemical reactions is reversible catalysis, which facilitates bidirectional reactions, enabling them to proceed efficiently even with minimal deviations from an equilibrium. This principle is essential for understanding the electrochemical dynamics of redox reactions, where metallic surfaces and molecular catalysts play crucial roles [172]. The integration of electrochemical processes in biological systems has been explored through electrochemically active bacteria (EAB), which can sense and respond to electrode potentials, thereby modulating their catabolic pathways. This ability to influence biochemical pathways via electrochemical signals opens exciting new possibilities for biotechnological applications [173]. Additionally, the role of redox mediators in electrochemical systems is critical. These mediators enhance the performance of energy storage and conversion systems by facilitating charge transfer processes. Advancements in redox mediator design can dramatically improve the efficiency of electrochemical systems, reducing reaction polarization and boosting overall performance [174]. As described above, the mechanisms of electrochemical modulation in biochemical reactions are diverse and far-reaching, spanning applications from biological systems to synthetic catalysis. These advancements not only deepen our understanding of electrochemical processes but also lay the groundwork for new technologies with wide-ranging applications.

6.1.2. Electrochemical regulation of molecules in biological processes

In addition to their sensing capabilities, electrochemical techniques offer a means to control biological activities by generating modulatory molecules at tissue or *in vivo* levels. By fine-tuning parameters such as electrode type and electrolysis conditions, these techniques allow targeted intervention in cellular and molecular processes, addressing both small molecules and macromolecules.

One approach involves the direct electrochemical synthesis or consumption of small modulatory molecules, including reactive oxygen species (ROS) [175, 176], nitric oxide (NO) [177], and ferricyanide [178], which influence gene expression and cellular signaling. Fussenegger et al. [175] introduced a DC-actuated regulation technology (DART) that enables electrode-mediated, time- and voltage-dependent transgene expression (Fig. 13a). In this system, ROS produced by DART activate NRF2, which translocates to the nucleus and binds antioxidant response elements (ARE) in synthetic promoters to coordinate antioxidant and anti-inflammatory gene expression. In a parallel study, Anikeeva et al. [177] developed Pt-Fe_3S_4 nanoclusters that electrocatalytically generate NO (Fig. 13b), modulating neuronal signaling by activating TRPV1 channels, and inducing Ca^{2+} influx, providing a technique *in vivo* to study NO's

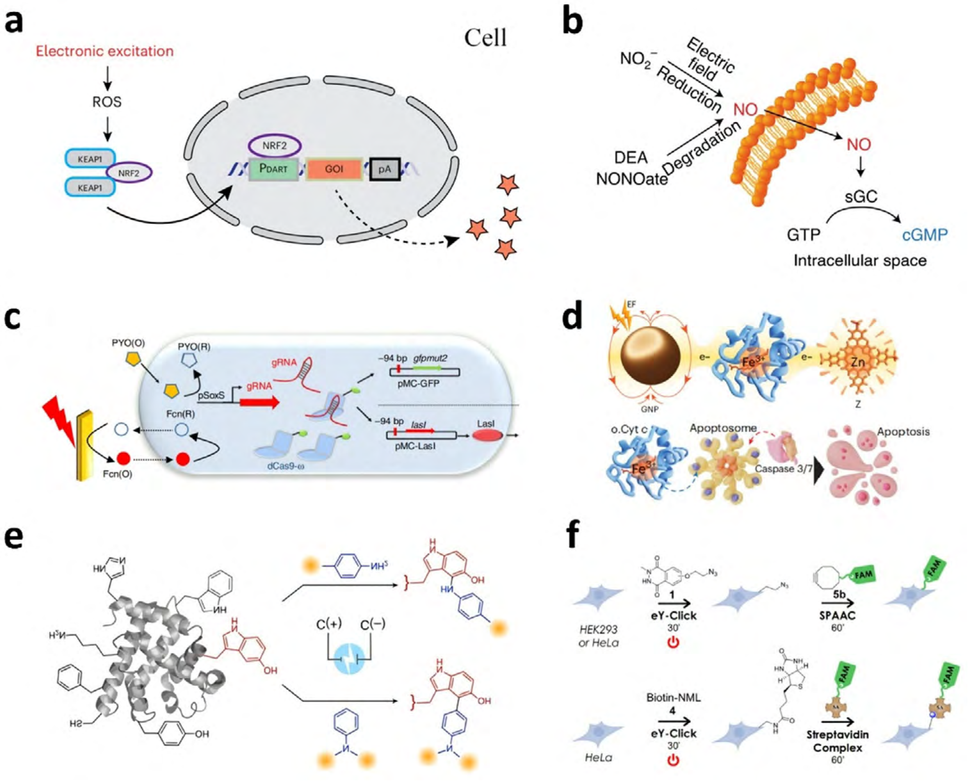

Fig. 13. Electrochemical platforms for programmable manipulation of cellular processes. (a) Schematic illustration of the electrogenetic circuit based on the NRF2/KEAP1 antioxidative response [175]. (b) Schematic illustration of the electrochemical NO delivery system and TRPV1 mediated Ca^{2+} influx [177]. (c) Schematic illustration of CRISPRa system in bacteria with electrical control over gRNA expression [178]. (d) Schematic illustration of the a.c. electric fields (EFs) inducing remote regulation of Cyt c redox state [179]. (e) Schematic illustration of electrochemical protein labelling strategies [180]. (f) Schematic illustration of Click-electrochemistry for the rapid labeling of cell surfaces [181]. Reproduced with permission of Refs. [175], and [177–181].

role in neurotransmission and other physiological processes. Bentley et al. [178] developed an electrogenetic CRISPR system (eCRISPR) with a SoxS-based promoter activated by pyocyanin and ferricyanide (Fig. 13c), allowing precise control the expression of guide RNAs and the formation of CRISPR-based transcription factor complexes.

Electrochemical techniques can also modulate macromolecules as well, particularly proteins, through redox states alteration [182] or chemical modifications [180, 181]. Rawson et al. [182] demonstrated a bio-nanoantenna constructed from gold bipolar nanoelectrodes functionalized with cytochrome c (Fig. 13d). Exposure to electrical inputs modulated the redox state of cytochrome c, triggering apoptosis in glioblastoma cells—a finding with promising therapeutic implications. In another study, Chatterjee et al. [180] developed an electrochemical labeling method (eCLIC) for site-specific protein labeling (Fig. 13e). This method is compatible with bioorthogonal reactions such as strain-promoted azide-alkyne cycloaddition (SPAAC) [181], expanding its applications in protein modification and engineering (Fig. 13f). These approaches offer promising strategies for controlling protein activity and, by extension, for modulating cellular processes in therapeutic contexts.

6.1.3. Electrochemical control of mitochondrial energy production

Mitochondria are central to cellular energy production through oxidative phosphorylation, a process driven by the electron transport chain (ETC) and ATP synthase. At the heart of this system is a tightly regulated electrochemical proton gradient across the inner mitochondrial membrane, which powers ATP synthesis. Advances in electrochemical methods have enabled real-time monitoring and modulation of these gradients, providing crucial insights into how mitochondrial energy production is controlled and how its dysfunction contributes to disease.

A core element of this electrochemical control is the mitochondrial membrane potential ($\Delta\psi$), generated by proton pumping through ETC complexes. This potential is essential for driving ATP synthase activity. Techniques such as positron emission tomography (PET) using voltage-sensitive radiotracers have revealed how $\Delta\psi$ varies within and across tissues, uncovering functional heterogeneity in mitochondrial bioenergetics. Notably, in cancer cells, dysregulation of $\Delta\psi$ disrupts normal energy metabolism, underscoring how electrochemical control is altered in disease states [30].

Electrochemical regulation also operates through calcium signaling, which directly influences mitochondrial bioenergetics. The electrochemical gradient across the mitochondrial membrane facilitates calcium uptake into the matrix, where calcium levels modulate key dehydrogenases and oxidative phosphorylation. This calcium-driven tuning of energy production reflects a dynamic electrochemical feedback loop. When disrupted, as in cardiac or neurodegenerative diseases, the result is inefficient ATP production and cellular stress [31].

Mitochondrial fusion and fission dynamics provide another layer of electrochemical regulation. Changes in mitochondrial morphology can affect the distribution and maintenance of membrane potential, altering how efficiently mitochondria respond to energy demands. Excessive fission may dissipate electrochemical gradients, leading to metabolic dysfunction, whereas regulated fusion supports gradient preservation and bioenergetic stability. Thus, electrochemical control is intimately linked to mitochondrial shape and network dynamics [32].

Sirtuins, particularly mitochondrial sirtuins (SIRT3, SIRT4, and SIRT5), are NAD^+-dependent enzymes that fine-tune mitochondrial function through deacetylation and other post-translational modifications. Their actions influence the ETC, ATP production, and antioxidant defenses. Since NAD^+ is itself a redox cofactor, sirtuin activity connects metabolic and redox states to electrochemical control, enabling mitochondria to adapt energy production to changing cellular conditions [183].

Another emerging layer of electrochemical control involves oxidative post-translational modifications (Ox-PTMs) of mitochondrial proteins, including ATP synthase and ETC components. These redox modifications can alter protein conformation and function, fine-tuning ATP production efficiency. In conditions such as heart failure, disrupted redox balance affects these modifications, leading to impaired mitochondrial electrochemical gradients and reduced energy output [184].

Finally, the energetic state of mitochondria, governed by ATP availability and membrane potential, influences the biogenesis of key respiratory complexes. For example, the proper assembly of complex III depends on ATP binding and hydrolytic activity. Disruptions in these processes feedback to impair electron flow and gradient generation, highlighting how enzyme assembly is part of the electrochemical regulation network [185].

In conclusion, mitochondrial energy production is governed by a tightly integrated system of electrochemical controls—ranging from membrane potential and calcium flux to redox regulation and structural dynamics. These mechanisms not only sustain efficient ATP generation but also offer promising targets for therapeutic intervention in diseases marked by mitochondrial dysfunction.

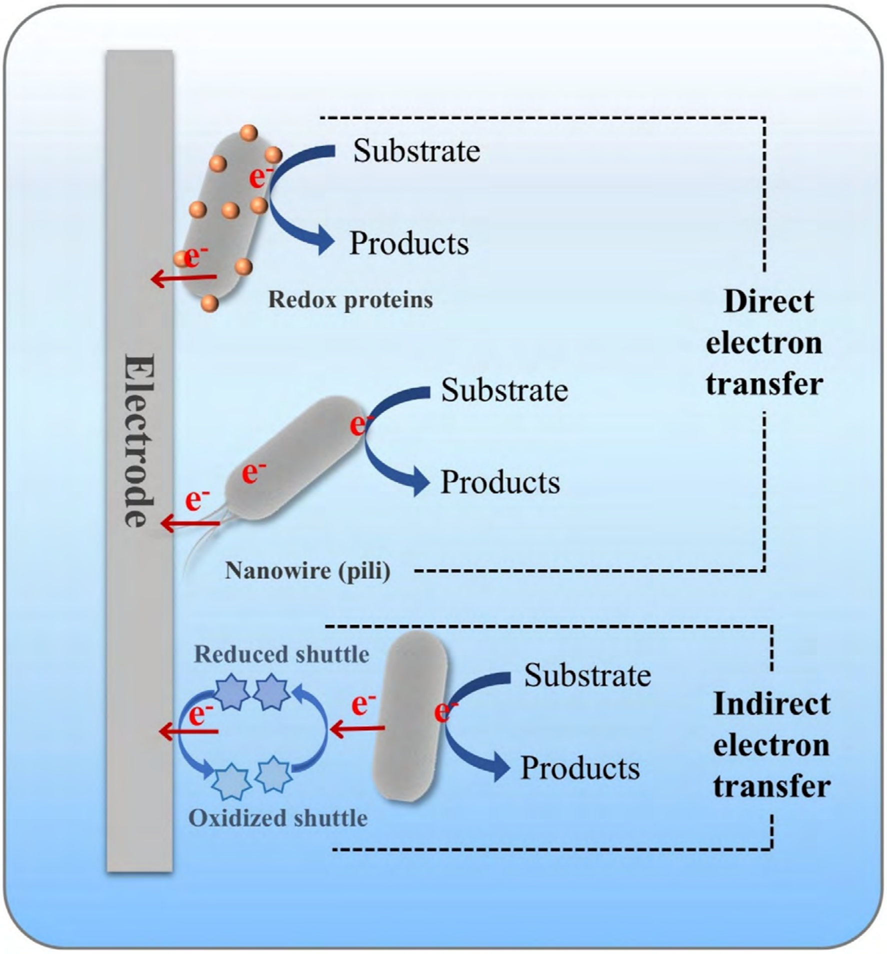

Fig. 14. Extracellular electron transfer mechanisms of electrochemically active microorganisms.

6.2. Electrochemical intervention in microbial and biomolecular functions

6.2.1. Microbial extracellular electron transfer

Extracellular electron transfer (EET) refers to the transfer of electrons from the microbial cell to an extracellular terminal electron acceptor across the cell membrane, or conversely, the transfer of electrons from an extracellular electron donor to the cell for metabolic utilization. The EET of microbes holds significant potential for applications in bioenergy-electricity conversion, bioleaching, bioelectrosynthesis, and environmental pollution remediation [186].

The EET mechanisms of microbes include direct and indirect electron transfers (Fig. 14). Direct electron transfer involves the transfer of electrons between microorganisms and extracellular electron acceptors through redox proteins located on membrane of microorganisms such as *c*-type cytochromes and conductive nanowires [187]. Indirect electron transfer involves the use of self-secreted endogenous electron mediators or exogenous electron mediators by microbes to transfer electrons to extracellular electron acceptors. Endogenous electron mediators include compounds such as phenazines and flavins, while exogenous electron mediators include substances like humus [188]. Microbial metabolic pathways can be modulated through targeted regulation of the aforementioned specific proteins and electron shuttles in the respiratory chain system.

6.2.2. Genetic engineering to regulate electron transfer of microbial metabolism

Genetic engineering is a powerful approach to enhance electron transfer efficiency and optimize microbial metabolic processes by designing and restructuring the metabolic pathway [33]. The proposed strategies include: (1) Enhancing the expression of *c*-type cytochromes, reconstructing *c*-type cytochrome maturation genes, and increasing the secretion of mature soluble *c*-type cytochromes to the cell surface or extracellular polymeric substances that can facilitate their participation in direct electron transfer. (2) Promoting conductive nanowires synthesis, modifying conductive nanowires genes, and engineering conductive nanowires structures, such as constructing organic-inorganic hybrid conductive filaments. (3) Enhancing the synthesis of endogenous electron mediators through gene clusters encoding these mediators and facilitating their excretion via the introduction of porin proteins.

Extracellular electron transfer functions as a tunable interface between the metabolism of living cells and the properties of synthetic materials. Through genetic and metabolic programming integrated with engineered electroactive living materials, material properties can be precisely regulated, enabling the development of materials with advanced sensing capabilities [34]. The study demonstrated the feasibility of controlling the expression of *Shewanella oneidensis* EET genes using programmable transcriptional regulatory genetic Boolean circuits. This approach enables the regulation of electron transfer flux from *S. oneidensis* to copper catalysts, precise control of hydrogel crosslinking, and the design of computational polymer networks responsive to multiple molecular combination signals, showcasing the potential to mimic physiological behaviors in engineered electroactive living materials. Engineered electroactive living materials have also demonstrated potential for the efficient reduction of uranium U(VI). By employing genetic engineering, uranium-binding proteins were integrated into the surface of *S. oneidensis*, and the Mtr transmembrane electron conduit pathway was reconstructed. Additionally, a biofilm promotion circuit was constructed to enhance cell-to-cell interactions, enabling the self-assembly of electroactive living materials under various conditions. This system demonstrated high efficiency and stability in uranium U(VI) reduction and capture, validating its applicability in uranium recovery [189].

Additionally, genetic engineering can be utilized for the intelligent reprogramming of microbial populations to regulate EET. A quorum sensing-based population-state decision system was designed and constructed, enabling the intelligent and dynamic reprogramming of cellular resource allocation based on the state of the bacterial population. In the initial stage, the system prioritizes diverting cellular resources toward cell growth. Once the population biomass reaches a critical threshold, the system reallocates resources to the expression and enhancement of EET functional genes. This approach optimizes the use of limited cellular resources and enables dynamic regulation of EET. The EET-reprogrammed strains developed using this system achieved up to a 4.8-fold increase in EET efficiency and demonstrated substantially enhanced pollutant reduction capabilities, with an 18.8-fold improvement in methyl orange degradation efficiency and a 5.5-fold increase in hexavalent chromium reduction efficiency [190].

6.2.3. Nanomaterials to regulate electron transfer of microbial metabolism

The nanomaterial-microorganism hybrid system is designed to maximize the efficiency of EET, regulate metabolic networks and implement programmable microbial functionalities. Its core strategy involves constructing artificial conductive channels to strengthen the electron connectivity and transfer at biological/abiotic interface. Electrochemically driven nanomaterial-microorganism hybrid systems can be categorized into exogenous and endogenous nanomaterial-microorganism systems. Exogenous nanomaterial-microorganism systems are established by incorporating nanomaterials (such as graphene and carbon nanotubes) into microbial systems. These nanomaterials, with their high conductivity and large specific surface area, enhance the electron transfer rate and range, thereby improving the overall electron transfer efficiency of the system. Endogenous nanomaterial-microorganism systems are synthesized by microorganisms through direct or indirect processes, operating under mild reaction conditions with high biocompatibility. These endogenous nanomaterials can be classified into the following types: single-metal nanomaterials, such as Pt and Pd; non-metal nanomaterials, including B, Te, and Se; bimetallic or multimetallic nanomaterials, such as Pd-Pt bimetallic nanoparticles; and metal compound nanomaterials, comprising metal sulfides and metal oxides [191]. The effective combination of microbes and materials is fundamental to achieving the functionality of microbe-material hybrid systems. Based on the binding position, and mechanism between microorganisms and materials, the interactions can be categorized into two types: intracellular and extracellular interactions. These interactions encompass specific mechanisms such as cell uptake, intracellular assembly, extracellular mineralization, electrostatic adsorption, and cell encapsulation [192].

Nanomaterials integrated with microorganisms can be distributed across intracellular, periplasmic, and extracellular regions. The incorporation of nanomaterials into these regions can enhance direct electron transfer via conductive nanowires or cytochromes, as well as facilitate indirect electron transfer through soluble electron mediators, which reduces electron transfer resistance and improves electron transfer efficiency at the biological/abiotic interface [193]. Nanoparticles can be synthesized through interactions with microorganisms via membrane-bound proteins (*c*-type cytochromes) or oxidoreductases. These synthesized nanoparticles form a conductive matrix that accelerates electron transfer. Additionally, nanomaterials can strengthen electronic interactions with the active centers of outer membrane *c*-type cytochromes, such as porphyrin iron, thereby facilitating the efficiency of electron absorption from cytochromes. This optimized electron uptake elevates microbial redox metabolic flux, manifesting as enhanced rates of metal reduction, nitrate conversion, and system power density in bioelectrochemical applications [194, 195]. Nanomaterials can also serve as nanowires to accelerate EET. Owing to their high conductivity, biocompatibility, and interconnectivity, synthesized nanomaterials integrate with bacterial cell membrane, efficiently transferring electrons from microorganisms to electrode surfaces in a manner similar to conductive nanowires, thereby enhancing bioelectricity generation [193].

Nanomaterials can also regulate EET and associated microbial metabolic functions through (1) sequestering microbial redox mediators, as observed in carbon-based nanomaterials (e.g., graphene, carbon nanotubes), and (2) serving as direct electron shuttles, such as nanocrystalline metal-oxide. Carbon nanomaterials enhance the concentration of electron mediators around the electrode by adsorbing bacteria and supporting the formation of dense biofilms, which shortens the diffusion distance of electron shuttles and optimizes the EET process [196]. Exogenous metal oxides function as exogenous electron shuttles, compensating for deficiencies in endogenous *c*-type cytochromes by establishing a transmembrane electron transfer network [197]. Concurrently, nanomaterials promote long-range electron transport across biofilms via aforementioned mechanisms, thereby amplifying interspecies electron transfer efficiency in syntrophic microbial consortia. This enhanced electron flux optimizes the kinetic parameters of redox processes, demonstrating significant application potential in anaerobic digestion, wastewater treatment, and environmental remediation [193, 197].

6.3. Electrochemical strategies for regulating neural signaling and function

Bioelectricity serves as an endogenous electrostimulation mechanism that modulates cellular and tissue behaviors, naturally occurring in electromechanically responsive tissues. Over the past decade, conventional metal electrode-based systems have significantly advanced our understanding of neural activity through electrical recording and stimulation [198]. Recent developments in semiconducting polymers and electrochemical transistors have further enhanced biological interface technology, enabling higher precise measurements and expand capabilities for complex *in vivo* applications. Moreover, the bioelectrical behavior could be regulated by external electric and mechanical stimulations. Mechnosensitive modulation of biological membranes and ion channels has been demonstrated to influence biological excitability [199]. These findings have spurred significant interest in developing novel approaches to control bioelectrical processes, and their downstream biochemical functions through innovative regulation strategies.

6.3.1. Regulation of biofunctions based on implantable flexible devices

Electrical stimulation is a powerful tool in neuroscience research and neural disease therapeutics.[35] This methodology generally relies on electrodes to facilitate charge-to-ion conversion at the interface between electrode and tissue, a vital process for triggering membrane depolarization and precisely modulating bioactivity. Traditional solid-state electrodes used widely present substantial limitations including mechanical instability and cytosol dilution effects, frequently inducing neuroinflammatory cascades following intracranial implantation [36]. Furthermore, persistent challenges emerge with chronic electrode implantation, where progressive gliosis elevates stimulation threholds, necessitating higher operating voltages. Such voltage increases might give rise to electrolytic water dissociation and consequent reactive oxygen species (ROS) production at the electrode surface, ultimately leading to localized microenvironmental disruption and tissue damage. In order to achieve the stable device-biological interfaces capable of highly efficient signal transmission in biological systems, three key requirements are necessary during construction of the applicable neural devices, including low modulus, low specific interfacial impedance, and high electrical conductivity. Minimizing the mechanical mismatch between tissue and implanted electronics is particularly crucial for eliminating immune responses and ensuring compatbility with natural body movements. Flexible microelectronic systems that emulate the mechanical properties of biological tissues offer distinct advantage, enabling both stable integration and electrical coupling with target populations for localized stimulation [200]. Notably, the design of implantable soft electronics with modulus values approaching ~10 kPa remains a challenge because of the limited availability of suitable electronic materials that combine the required mechanical and electrical properties.

To address these challenges, various conductive flexible materials were created for implantable bioelectronic devices capable of precies biofucntion modulation [200–205]. Among these, flexible polymer substrates have emerged as promising alternative to conventional silicon and carbon fiber electrodes. Thanks to their tissue-mimicking mechanical properties, hydrogels have gained widespread adoption in cell cultures, and soft tissue implantations [201]. However, the traditional ionic hydrogel face fundamental limitations in neural applications, including poor electronic conductivity and the sluggish ion that prevent resolution of high-speed, and single-neuron-single-spike activity. To solve this limitation, Bao and colleague pioneered an innovative approach by developing a conductive ion gel through blending ionic liquid into with poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate)(PEDOT:PSS) [200]. Subsequent water exchange transformed this material into an electrically conductive hydrogel with micropatterned architecture. The resulting material demonstrated exceptional performance metrics, including high current density, and low impedance, enabling successful sciatic nerve stimulation *in vivo* (Fig. 15a). Despite these advances, such hydrogels were rarely introduced into biosensors for chemical monitoring, probably due to the difficulty in specific chemical recognitions. To further improve the functions of flexible electric devices to regulate biofunctions, Peng et. al developed a soft fiber neural device capable of stably tracking individual neurons in the deep brain of medium-sized animals under vigorous activity [202]. Inspired by the axon architecture, this fiber neural device is constructed with a conductive gel fiber possessing a network-in-liquid structure using conjugated polymers and liquid matrices, and then insulated with soft fluorine rubber. This strategy reconciles the contradictions and simultaneously confers the fiber neural device with low modulus down to 300 kPa, low specific impedance of ~579 kΩ·μm^2, and electrical conductivity ~ 3 times higher than hydrogels. This multifunctional device achieved stable single-unit neural recording in freely moving cats, demonstrating unprecedented performance in large animal models during vigorous activity.

Beyond conventional implantable electrodes, self-powered bioelectronic devices capable of harvesting and storing biochemical energy have become a promising way for biofunctional modulation through electrical stimulation. These devices offer distinct advantages for eliminating the need for external power sources, leveraging physiological energy gradients, and enabling sustained bioelectronic intervention. However, these miniaturized implants often were hindered by limited power density. To address this challenge, Peng et. al developed an implantable fiber bio-supercapacitor with high power density [206]. The device was fabricated by twist-assembling multi-strand CNT fibers into integrated energy harvesting and storage modules (Fig. 15b). This innovative architecture provides multiple ion transport channels and a large electrochemically active surface area, enabling efficient mass diffusion and rapid charge transfer across electrodes. In a glucose solution within the physiological concentration, the fiber bio-supercapacitor achieved a record-high power density of 22.6 mW·cm^{-2}, and demonstrated robust electrochemical stability under continuous pulsed operation and dynamic mechanical deformation. Following subcutaneous implantation in rats, the fiber bio-supercapacitor exhibited excellent biocompatibility and successfully delivered electrical stimulation to the sciatic nerve, highlighting its potential for long-term bioelectronic therapies. With the flourishing of semiconducting polymers and electrochemical transistors in the recent years, neural recording and stimulation get more opportunities to detect more precisely and applicable for more complicated *in vivo* sensing. Organic electrochemical transistors (OECTs) are recently developed high-efficient transducers not only for electrochemical biosensor but also for cell electrophysiological recording due to the separation of gate electrode from the transistor device [207]. Coupling of OECTs with *in vivo* electrophysiological recordings is necessary and beneficial for brain-machine interfaces. The organic transistors with conducting channels can connect both electronics and ions within the electrolyte. Ions can penetrate into the volume of the polymer channel and compensate the semiconductor, which will consequently change the conducting ability and thus modulate the current density of the channel. The device, with an OECT embedded on a thin organic film, recording *in vivo* epileptiform discharge, and performing great signal-to-noise ratio compared with state-of-the-art surface electrode. In addition, the OECTs can record the low-amplitude activities on the surface of the brain, which was superior to the traditional surface electrodes, which holds promising future for medical applications (Fig. 15c).

6.3.2. *Regulating biofunctions by mechanical stimulations*

The functions of mechanosensitive membrane proteins in sensory neurons, including Piezo receptors in touch-sensitive neurons and transmembrane channel-like receptors in auditory hair cells, have widely investigated [190]. Mechanosensitivity can be described as the complex interplay between proteins that enable cells to sense, transduce, and respond to mechanical stimuli and properties of their environment. Conversely, neuronal activity can be modulated by mechanical stimuli. To date, some techniques were developed to realize the mechanical stimulation to neurons. Benjamin et. al mechanically stimulated rat cortical neurons in ensemble by shear stress, as

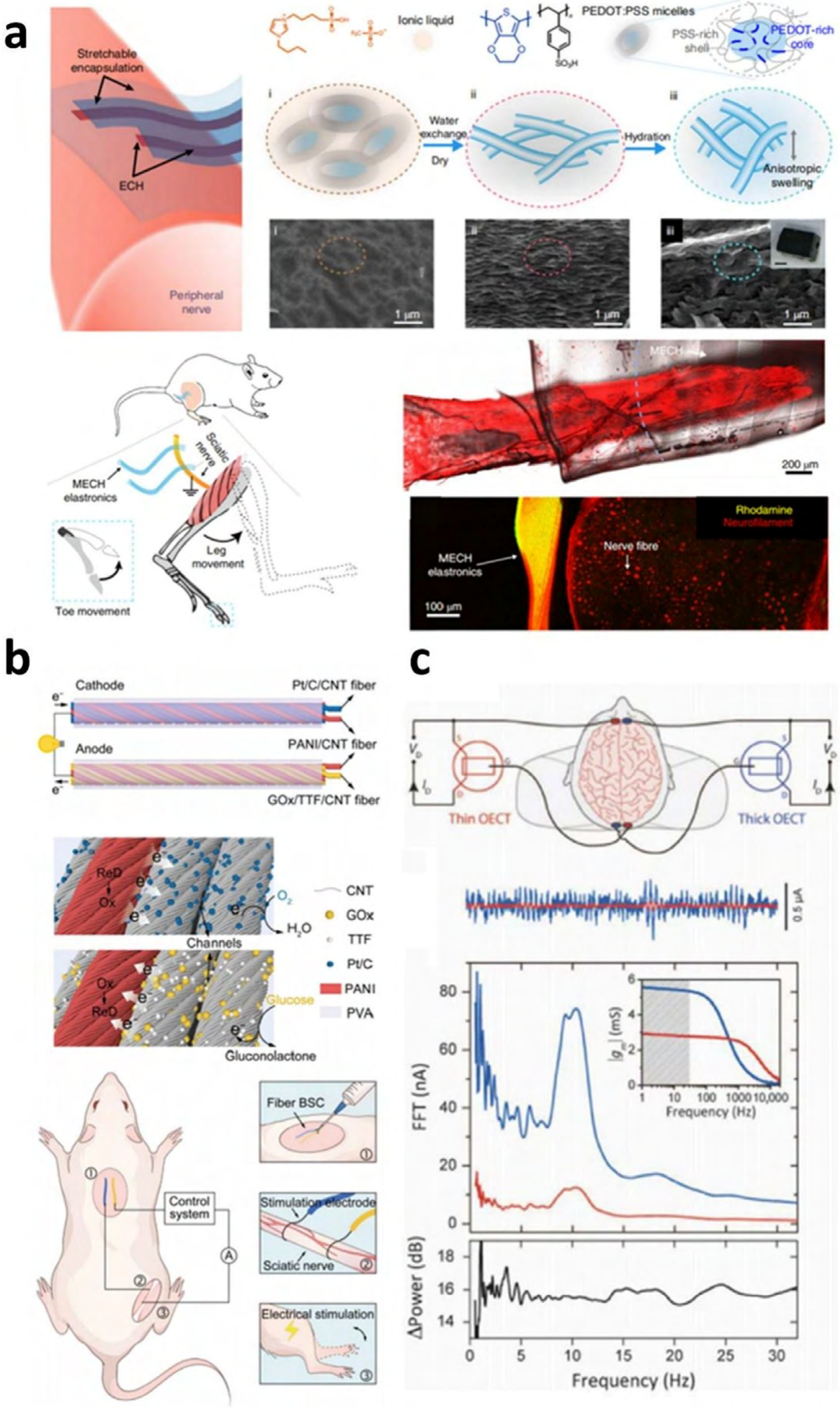

Fig. 15. Biointegrated electroactive platforms for neuromodulation and neural recording. (a) Schematic illustration of an ECH and stretchable encapsulation material with tissue-level Young's modulus, along with the in vivo neural stimulation experiment with a MECH microelectrode [200]. (b) Schematic of fiber BSC construction, working mechanisms, implantation and electrical stimulation of the sciatic nerve in a rat [206]. (c) Schematic wiring of simultaneously recording human EEG signals by two OECTs, demonstrating the enhanced EEG signal acquisition enabled by high-transconductance OECTs [207]. Reproduced with permission of Refs. [200], [206] and [207].

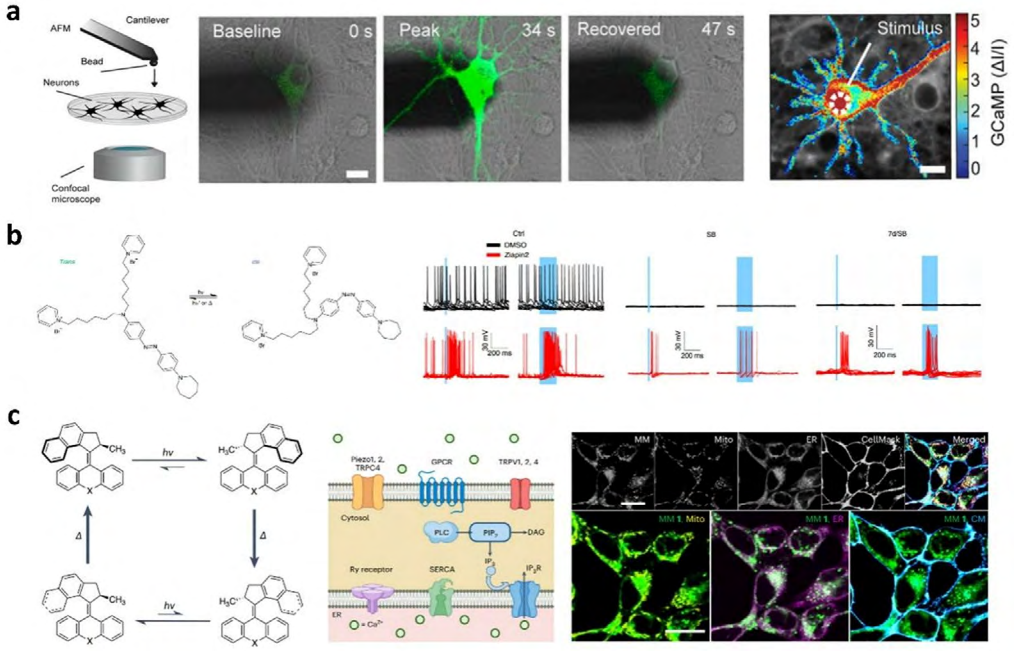

Fig. 16. Multimodal interfacing tools for spatiotemporally controlled neuromodulation and mechanotransduction studies. (a) Schematic of the coupled AFM and confocal microscopic system, the evolving states of cortical neurons under mechanical stimulation, and the calcium response triggered by the stimulus [199]. (b) Schematic of the isomerization process in Ziapin2 and the light-evoked firing activity in primary neurons loaded with Ziapin2 [210]. (c) The structures and mechanism of rotation of MM and the mechanistic study of calcium waves induced by MM [211]. Reproduced with permission of Refs. [199], [210] and [211].

well as subcellular compartments of single neurons by AFM-based local indentation [183]. Using an AFM-based cell mechanical assay in combination with confocal and super-resolution microscopy (Fig. 16a), neurons were found to show 2 distinct responses, classified as transient and sustained. Transient responses display fast kinetics, similar to spontaneous neuronal activity, whereas sustained responses last several minutes before returning to baseline. Local soma stimulations with micrometer sized beads evoke transient responses at low forces of ~220 nN and pressures of ~5.6 kPa, and sustained responses at higher forces of ~360 nN and pressures of ~9.2 kPa. Among the neuronal compartments, axons are highly susceptible to mechanical stimulation and predominantly show sustained responses, whereas the less susceptible dendrites predominantly respond transiently. In this case, mechanically evoked responses require the influx of extracellular calcium through ion channels. To elucidate the dynamics of cellular membrane tension and its role in mechanosensing, a force-controlled nanopipette-based method was developed through combining fluidic force microscopy with fluorescence imaging for precise manipulation of the cellular membrane tension [183]. The force-controlled nanopipette enables control of the indentation force imposed on the cell cortex as well as of the aspiration pressure applied to the plasma membrane. This setup can be used to concurrently monitor the activation of Piezo1 mechanosensitive ion channels via calcium imaging. Moreover, the spatiotemporal behavior of the tension propagation is assessed with the fluorescent membrane tension probe Flipper-TR, and further dissected using molecular dynamics modeling.

Inspired by natural bio-piezoelectric phenomenon, efforts have been devoted to exploiting high-performance piezoelectric biomaterials, which can directly convert mechanical pressure into electrical response under ultrasonic stimulation [208, 209]. Through the electric field, holes and electrons of the material are well separated, activating piezoelectric catalytic oxidation-reduction reaction. Meanwhile, piezoelectric potential generated by piezo-electric biomaterials can tilt energy bands, and alter the potential of valence and conduction band edges, thereby improving redox capabilities. Under ultrasound or other external stimuli, piezoelectric materials can generate an electric field to produce reactive oxygen species (ROS), inducing cancer cell apoptosis [209]. For example, $BaTiO_3$ nanoparticles generate O_2 and ROS via piezoelectric catalysis to alleviate tumor hypoxia and kill cells; the $Cu_{2x}O$-$BaTiO_3$ heterojunction acts as both a sonosensitizer and chemodynamic agent to enhance ROS production; Se-doped KNN piezoelectric ceramics disrupt cell membrane potential homeostasis to promote intracellular Se-driven ROS generation and activate the caspase-3 apoptotic pathway. Additionally, piezo-photocatalytic therapy enhances redox reactions by facilitating interfacial electron separation, further killing cancer cells. Piezoelectric catalytic sensors exhibit extensive applications in physiological signal monitoring and *in vivo* biomolecular detection, owing to their highly efficient catalytic reactions, exquisite sensitivity, unique mechano-electrical transduction properties, and self-powered capabilities.

On the other hand, some smart molecules were designed and employed to generate mechanical stimulation to cells and the living animals. Current mechanical stimulation molecular strategies can be broadly divided into two categories: molecular switches, and molecular motors [210–212]. Molecular switches generally exist in two distinct states that are reversibly interconverted upon application of an external stimulus. The typical examples are azobenzene and its derivatives, which undergo cis-trans isomerization under light exposure. A photosensitive azobenzene compound (Ziapin2) was designed to stably embed into cell membranes and induces membrane thinning through trans-dimerization in darkness, thereby increasing membrane capacitance at steady state (Fig. 16b) [210]. In neurons loaded with this compound, millisecond-scale visible light pulses elicit transient hyperpolarization followed by delayed depolarization, triggering action potential firing. These effects persist and can be induced *in vivo*, showcasing the potential of Ziapin2 to modulate membrane capacitance on millisecond timescales without directly affecting ion channels or local temperature. In addition, molecular motors have emerged as a promising nanoscale tool for cellular mechano-regulation (Fig. 16c) [211]. These light-activated organic rotary motors enable unidirectional 360° rotation of a part of the molecule around an internal axis. In recent years, MMs have been employed to stimulate calcium ion release from the endoplasmic reticulum, achieving regulation of cardiomyocyte contraction.

6.4. New paradigms for electrochemical treatment of related diseases

Strong single pulse electric field can damage the cell wall, and electroporate cell membrane to induce cell tissue necrosis, moreover, the electric fields or pulses with different intensities affect free radical reactions [213] and the synthesis of biomolecules such as DNA [214] in living cells, accompanied by subsequent phenomena, including the regulation of cell growth [215], which leads to new paradigms for electrochemical treatment of related diseases. The pioneering direct electrochemical therapy for tumors was reported in 1983 by Nordenstrom group, who proposed the theory of vascular interstitial biological closed circuit [216]. The short pulses of high voltage current can lead to cell death without heat effects, and result in irreversible electroporation and pore formation within cell membranes. Subsequently, Heller [217] combined the electrical permeability with chemotherapy by applying an electric pulse of 1.5 $kV\cdot cm^{-1}$ for 90 μs to melanoma C57BL/6-bearing mouse with injection of 0.25 U erythromycin to enhance tumor cell uptake and reduce the dosage of chemotherapy drug, leading to an indirect electrochemical therapy strategy. The indirect electrochemical strategy has been used to deliver charged drug molecules by redox flow iontophoresis at an applied voltage, where a redox mediator solution is used to control electrode reactions and sustain continuous delivery for theoretically unlimited duration, allowing solvent-free delivery directly into the site of interest and overcoming issues associated with systemic exposure to the drug [218]. This concept enables the continuous delivery of various potent drugs into the brain and spinal cord, and therefore, has the potential to improve treatment options for various diseases. Thus the electricity-based or electrochemical approaches have entered in the category of local therapy. The mechanism probing of chemotherapy combined with electrical pulses (such as optimal electric field intensity and minimum effective dose) and the impact of electromagnetic fields on cellular systems [219] is a meaningful research field in clinical applications.

Cellular redox homeostasis is essential for maintaining cellular activities. Transplasma membrane electron transport systems composed of oxidoreductase enzymes play an important role in maintaining this balance. The continuous electrochemical therapy or electrochemical red-ox therapy can be operated at a low voltage (<15 V) with an application of the direct current (mA) using thin electrodes embedded within tumors and destroying them in less than 2 h. Its killing capacity relies on electrochemical reduction-oxidation reactions or “electrolysis” events [220] rather than electrical “shocks” due to ohmic or heating effects, electrical charge accumulation and electroporation of cell membranes. This treatment technique has been rapidly developed to modulate the intracellular redox state via external electrical field polarization [221], or extracting intracellular charges [222]. For example, Chevalier’s group used 2 stainless steel electrodes vs. 4 platinum-iridium (Pt-Ir) electrodes to deliver current densities of 10–35 $mA\cdot cm^{-2}$ to human PC-3 and LNCaP tumor xenografts growing subcutaneously in nude mice for 30 or 60 min and achieved the assess of electrochemical therapy efficacy for prostate cancer [223]. Rawson’s group has proposed a series of pioneering work to modulate the intracellular redox state using conductive materials. They achieved modulation of intracellular chemistry in a "wireless" manner based on bipolar behavior, and combined the wireless nano-electrochemical tools with cancer cells to successfully trigger cancer cell death [179]. Mao's group used graphene microsheets to construct transmembrane electrodes for cell membrane penetration, and achieved excellent transmembrane tunnel for electron flow and the regulation of intracellular ROS) and NADH [224]. This method provides a wireless and electric-field-free approach to modulating cellular redox states, which can be further applied in intervening cell processes and treating neurological diseases.

Electrochemical therapy has been extensively studied in cartilage [37] and more recently applied to skin [38]. In a method proposed by Wong's group [39], Pt electrodes were inserted into soft tissue to apply an electrical potential for redox reactions and the electrolysis of either endogenous tissue water content or injected normal saline, which generated highly localized pH gradients (acid and base) *in situ*, and led to a number of effects in soft tissue, including the alteration of skin biomechanics, and denaturation of dermal collagen, providing valuable protocol for the treatment of hypertrophic scars and keloids.

The electrochemical behaviors of living cells, such as the electron transfer between the cell active centers [225], depend on their physiological activity. Therefore, the monitoring of electrochemical behaviors provides simple and rapid measurement protocols for studying the responses of tumor cells to anticancer drugs [226]. The electrochemical methods based on the behaviors of living cells can save costs, reduce operational steps, and improve the sensitivity for screening anticancer drugs, leading to a reliable drug sensitivity testing technique for treatment of related diseases. This technique was early performed by using a MWNTs modified electrode to accelerate the electron transfer between the cell active center and electrode for comparing the sensitivity of several anti-tumor drugs to tumor cells [227]. An electrochemical approach was also proposed for rapid readout of the antibiotic susceptibility profile of a bacterial infection within one hour by monitoring the electrochemical reduction of a redox-active molecule to report the levels of metabolically-active bacteria [228]. This electrochemical phenotyping approach is effective with clinically-relevant levels of bacteria, and provides results comparable to culture-based analysis.

7. Outlooks

Electrochemistry is increasingly integrated with complementary methods and synthetic biology, opening new possibilities for both discovery and application. One important direction is multimodal analysis: pairing electrochemical sensors with spectroscopy or force microscopy links electron transfer dynamics to structural or mechanical changes in real time. Recent combinations of SECM with omics approaches, for example, have revealed how extracellular matrix stiffness shapes ferroptosis pathways [102]. Machine learning applied to multiplexed voltammetry promises to resolve complex neurochemical networks in diseases such as Parkinson's, potentially identifying destabilizing cascades before symptoms arise [155].

Future modulation of biology will focus on organelle and subcellular scales. Conductive nanomaterials like graphene microsheets can penetrate membranes and regulate redox states without conventional electrodes [224]. Self-powered bio-supercapacitors that harvest glucose as fuel have been used to stimulate peripheral nerves [206], suggesting routes toward autonomous metabolic implants. In synthetic biology, rewired electron flux enables engineered microbes to process pollutants or recover valuable metals, with quorum-sensing circuits dynamically optimizing extracellular transfer [189, 190].

Therapeutic applications are also advancing in precision. Nanoparticle-mediated electrochemistry generates radicals selectively within tumor microenvironments, avoiding systemic toxicity [229]. Devices that deplete oxygen can synergize with hypoxia-activated prodrugs to enhance cancer therapy [230]. Biohybrid implants linking ROS sensors with therapeutic gene circuits may evolve into self-regulating systems for inflammation control [175]. In neurology, organic electrochemical transistors (OECTs) are emerging as soft, biocompatible interfaces capable of detecting seizure precursors *in vivo* [207], providing a foundation for closed-loop neuromodulation.

Fundamental questions remain. Ultrafast electrochemistry combined with spectroscopy can probe quantum phenomena in photosynthetic charge separation, while nanopipette arrays may reveal mitochondrial redox heterogeneity relevant to aging. Single-vesicle ECL microscopy already visualizes neurotransmitter release [101], but extending electrochemical readouts into intraorganelle space remains a major challenge. Progress will depend on overcoming barriers such as biofouling [88] to enable stable, long-term *in vivo* measurements [98].

Scaling biohybrid electrocatalysis and improving device durability are further translational hurdles. Sporomusa–solar cell hybrids that reduce CO_2 to multicarbon fuels [56] illustrate promise, but viability depends on optimizing biotic–abiotic interfaces at the nanoscale [193, 197]. For clinical applications, chronic implants must be both soft and antifouling:

modulus-matched hydrogels minimize scarring [92], while zwitterionic coatings prevent protein adhesion [89], both essential for long-term performance in neural systems [200].

Looking ahead, electrochemical biology is poised to unify mechanistic insight with practical intervention. By probing quantum effects in enzymes, resolving organelle-level redox heterogeneity, and integrating real-time biosensing with adaptive therapeutic systems, this field offers a roadmap to both decipher and engineer life at unprecedented precision. Continued advances in biohybrid devices, nanomaterials, and synthetic biology will expand the reach of electrochemistry—from understanding fundamental energy conversion to enabling autonomous, targeted biomedical interventions—positioning the discipline at the forefront of next-generation biology and medicine.

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Author contributions

All authors equally contributed to this work.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on reasonable request.

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对十大科学问题之七“如何破解生命过程中电子传递、能量/物质转化及其与人类疾病的关系和电化学调控原理?”的深度思考——

生命过程的电化学表征与调控

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摘要:

电化学过程是生命功能的核心, 主导着能量转导、代谢流动与分子信号传递。随着电化学科学的快速发展, 如今能够以空前的空间、时间与化学分辨率对这些过程进行探测与调控。本综述构建了一个从基础机制到表征技术再到功能调控的整体框架。本文首先概述线粒体呼吸、微生物胞外电子传递和DNA 与蛋白质介导的电荷传导途径, 并介绍光合作用中的光-电子转换原理, 以及氧化还原平衡在协调细胞响应中的核心作用。随后, 重点总结可实现多尺度生命体系表征的电化学分析技术, 包括生物传感、电化学与扫描探针成像、电化学发光检测, 以及膜电位与神经递质的动态测量。随着柔性生物界面、超微电极与纳米孔等新兴平台的快速发展, 上述表征和测量进一步扩展至体内和单分子尺度。最后, 本文讨论如何利用电化学调控代谢通路、微生物和蛋白质活性以及神经信号, 从而实现精准治疗和生物工程应用。总体而言, 这些进展确立了电化学作为解析与引导生命体系研究的强大基础工具。

关键词: 电化学分析; 单细胞电化学; 生物电子转移; 光合作用; 电化学生物传感