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Signal Amplification for Highly Sensitive Bioanalysis Based on Biosensors or Biochips

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As the development of life science and biomedical science, the detection of biomolecules with low abundance and the acquisition of ultra weak biological signals have become a bottleneck of these fields. Therefore, developing high sensitive analytical methods coupling with the specificity of biological recognition events is in urgent need [1]. However, owing to the inherent background signals of various instrumental analytical technologies and the limitation of the classical analytical methodologies, improving the sensitivities via traditional physical methods or simple chemical and biocatalytic processes is far from meeting the practical demands. The progress in nanotechnology and biotechnology set a convenient and promising way to develop novel analytical methods with high sensitivity. Recently, as a result, a series of novel signal amplification strategies have been designed based on nano and molecular biological methods [2]. By combining these strategies with biosensors and biochips, many practical bioanalytical methods and biosensing technologies have been proposed. The principles, techniques and applications in bioanalysis of these novel strategies are described as follows.

The first type of signal amplification strategies is nano signal amplification. It includes 6 ways. 1) Accelerating the electron transfer or obtaining sensitized optical signal by taking the advantages of good conductivity and unique optical characteristics of the nanomaterials. The typical examples are the applications of carbon nanomaterials such as carbon nanotubes, grapheme, carbon nanohorns carbon nanofiber, nitrogen-doped carbon nanotubes, and metal nanoparticles such as gold nanoparticles. 2) Realizing optical, electrical or visual analysis by applying the catalytic and enzyme mimetic functions of the nanomaterials. This way has been applied in the analysis of small biomolecules, proteins and genes. 3) Developing stripping voltammetry, electrochemiluminescence, fluorescence or mass spectrometry analysis by using the nanomaterials as tag molecules [3,4]. The interesting example is the electro-chemiluminescent behaviors of quantum dots. These tags can be further amplified by ordered assembly, click chemistry or directly synthesizing the multiple quantum dots in the framework of dendrimer or polymer. 4) Nanomaterials are used as the carriers of signaling molecules, which includes both redox active molecules and optical molecules with fluorescence, or infrared, ultraviolet and Raman adsorption. Some catalysts such as enzymes are also the signaling molecules, because they accelerate the chemical or biological reactions to enhance the signals or produce the molecules with redox activity or optical character. 5) Taking the advantages of optical-electrical properties of nanomaterials to realize electro-chemiluminescent or photo-electrochemical signal amplification, which promotes the quick development of two new directions. 6) Selectively concentration of the biomolecules with low abundance by using biofunctionalized nanomaterials.

These novel signal amplification strategies have been used in electrochemical detections such as voltammetric analysis, impedance analysis, capacitance analysis, electro-chemiluminescent analysis and photo-electrochemical analysis; optical detections such as chemiluminescent analysis, fluorescent analysis and infrared, ultraviolet and Raman analysis; mass spectrometric analysis

and the development of imaging technologies such as grayscale scanning imaging, scanning electrochemical microscopy imaging, chemiluminescence imaging, fluorescence imaging, Raman spectral imaging and mass spectral imaging. When introducing these strategies to biosensors and biochips, the established methods can conveniently be used in the detections of small biomolecules, proteins, cells and the carbohydrate sites on cell surfaces [5]. Some methods can even realize quasi-single-molecule detection. By coupling with protein array and CCD, the developed chemiluminescence imaging techniques can greatly increase the detection channels and improve the detection throughput. Furthermore, by the competition between the primary target surface and the secondary signal surface and the following silver enhancement, an information transfer strategy has been proposed for the visualization of target. More recently, a method for target-cell-specific delivery, imaging and detection of intracellular microRNA with multifunctional nanoprobe has been proposed [6]. Unlike PCR amplification in DNA detection, there is no common amplification method in protein detection, which forms a great challenge. Now this challenge can be overcome by applying the signal amplification strategies mentioned above.

The second type of signal amplification strategies is based on molecular biological amplification. PCR amplification is the earliest applied technique in this category. It can conveniently amplify the DNA samples and the detection signal by using the product as detection target. Although, this technique has been achieved on the surface of biosensors and biochips, the problems such as complexity, potential contamination, high cost and the limited detection targets have limited its usage. By introducing the functionalized nanomaterials, novel technologies such as rolling circle amplification (RCA), target-induced repeated primer extension, hybridization chain reaction, loop-mediated amplification and target DNA recycling amplification including endonuclease, exonuclease and polymerase-based circular strand-replacement polymerization have been applied to amplify the electrochemical, optical and visual signals. For example, a cascade signal amplification strategy for sub-attomolar protein detection by RCA and quantum dots tagging. This strategy can quantitatively detect protein down to 16 molecules in a 100- μ L sample [7] and DNA to amole level, which greatly extends the detection range of electrochemical analysis. When applying these strategies in detection of low-abundant

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biomolecules, the field of bioanalysis gets access to the opportunity of vigorous development.

The high sensitivity brought by signal amplification makes it possible to detect undetectable targets by traditional methods, such as some disease markers, biological threat agents and pathogens. The application of novel nanomaterials and molecular biological technology is promising to further expand the tentacles of bioanalysis and promote the overall development of analytical science.

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