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Research Progress of Optical Biosensing Technology for Alpha-fetoprotein Detection

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Abstract: Alpha-fetoprotein (AFP) is intimately associated with the incidence and progression of liver cancer and various tumors. AFP exhibits elevated concentrations in various tumors, making it a viable positive detection marker for these malignancies. Consequently, the development of precise, ultra-sensitive, and highly selective AFP detection methods is crucial for the early detection and effective monitoring of these life-threatening diseases. Optical biosensors rank among the most efficient detection techniques currently available. These biosensors possess features such as low cost, high sensitivity, real-time monitoring, and non-invasiveness, making them more suitable for AFP detection compared to other methods. This article reviews the role of this novel biosensor in the early detection of AFP, which holds significant implications for cancer diagnosis.

1. Introduction

This macromolecular protein was first discovered in 1956 by electrophoresis of plasma proteins from placental tissue in two independent laboratories in San Francisco, USA, and was named Alpha-fetoprotein. AFP is a high concentration in fetal and maternal blood, and is closely related to the occurrence and development of liver cancer and a variety of tumors, in a variety of tumors can show high concentrations, can be used as a variety of tumors positive detection indicators[1]. Clinically, AFP is mainly used as a serum marker for primary liver cancer, and is used for diagnosis and efficacy monitoring of primary liver cancer.

In recent years, many analytical methods have been developed and used for AFP detection, such as: enzyme-linked immunoassay (ELISA)[2], fluorescence immunoassay (FLIS) [3], radioimmunoassay (RIA) [4], chemiluminescence immunoassay [5], etc. Fluorescence immunoassay and chemiluminescence immunoassay have been widely used in clinical detection due to their advantages of high sensitivity, good stability, and no radiation contamination. However, they require expensive detection instruments and high detection cost, so they are not suitable for screening serum AFP in a large range of people. Enzyme detection (ELISA), simple operation, has high sensitivity, does not need special instruments, low detection cost, suitable for natural population early liver cancer survey, is one of the important means to find early liver cancer. The shortcomings are that there are many influencing factors in the detection process, the repeatability is not high, the detection range is narrow, the judgment of the qualitative test results is affected by subjective human factors, and the standard curve must be made for each quantitative detection. In order to improve the reliability of the detection results and reduce the detection cost in clinical practice, ELISA method can be used to screen the serum AFP level in a wide range. If the result is positive, electrochemical luminescence immunoassay can be used for quantitative detection.

The optical biosensor can realize the energy conversion of biological information to optical signal, so as to realize the detection and analysis of biomolecules with high sensitivity and selectivity[6]. Most of them are constructed by immobilizing biomolecules (such as antibodies, RNA, RNA or DNA and enzymes) to the surface of a solid material (such as optical fiber) to convert the interaction of biological parts and target markers into quantifiable signals. Due to the high dependence of antibodies on their target, the combination of antibodies and antigens is considered to be an excellent strategy for detecting specific targets in human samples. Therefore, optical biosensors are widely used in the detection of biological macromolecules.

In this paper, the latest research progress of optical biosensor in the detection of alpha-fetoprotein is summarized. Finally, some challenges faced by optical biosensor systems in AFP detection are analyzed, and the prospect of optical biosensor systems in AFP detection is presented.

2. Optical Biosensor for The Detection of Alpha-fetoprotein

2.1. Local surface plasmon resonance biosensor

LSPR means that when the incident light shines on the metal Surface at a specific Angle, it will stimulate the free electrons on the metal surface to produce resonance phenomenon under the action of electromagnetic field, forming a Surface Plasmon Polariton. The generation of this resonance wave leads to the local enhancement of the electromagnetic field on the metal surface, which causes the change of the absorption, scattering or reflection characteristics of the light[7]. In the biosensor, the biometric element (such as antibody, nucleic acid, etc.) is fixed on the metal surface, when the target molecule is combined with the biometric element, it will cause the refractive index of the metal surface to change, thus affecting the LSPR resonance conditions, and the detection and analysis of the target molecule can be realized by monitoring the change of the incident light. In recent years, LSPR biosensors have been widely used in the detection of proteins. The emergence of nanomaterials has accelerated the application of LSPR in biosensors, and many efforts have been made to change the size and shape or arrangement of precious metal nanoparticles as well as the nanostructure. These techniques have sufficient selectivity and sensitivity for the determination of AFP, which greatly improves the detection limit of AFP. In 2016, Wang et al. developed a signal amplification strategy utilizing antibody quantum dot (QD) conjugate for sensitive and

quantitative detection of alpha-fetal protein (AFP), carcinoembryonic antigen (CEA), and cytokeratin fragment 21-1 (CYFRA 21-1) in clinical samples. They first increased signal amplification by 50 times using a dual signal amplification strategy of AUNP-antibody and antibody-QD coupler. The constructed SPR biosensor has detection limits as low as 0.1ng/mL for AFP, CEA and CYFRA 21-1. In addition, the results obtained using the SPR biosensor were consistent with those obtained using electrochemical luminescence methods. Therefore, the constructed SPR biosensor provides a highly sensitive and specific method for the detection of tumor markers. This SPR biosensor can be easily applied to the detection of other tumor markers and could provide a potentially powerful solution for tumor screening[8].

2.2. Fiber Bragg Grating biosensor

In FBG, mode coupling occurs in the forward and reverse transmission of the core layer guide mode. The characteristics of the Bragg grating are combined with biometric elements to achieve high sensitivity and real-time monitoring of biomolecules[9]. Fiber Bragg grating is widely used in various fields because of its good characteristics such as spectral selectivity, wavelength tunability, corrosion resistance and high sensitivity, and it is also very suitable for the detection of AFP. In 2023, Yang et al. developed a single-sided fiber cone fiber Bragg grating, which can improve the sensitivity and reduce the difficulty of manufacturing. The chirped grating is made on the taper of the reduced fiber, and the spectral resolution is improved by mediating the narrow linewidth signal through the local Fabry-Perot effect. In addition, the modification of plasma gold nanostars (AuNSt) on the grating sensor, due to the enhanced electromagnetic field induced by the star-shaped nanotip, further improves the sensitivity and significantly speeds up the electrostatic attraction mediated test. The biosensor responded to myocardial troponin-1 at a concentration of less than 10 ng/mL, with a LOD of 3pg/mL in buffer and 11.9pg/mL in clinical serum[10]. What's more, the required test time can be reduced to about five minutes. The results of tests on clinical serum samples further validate the effectiveness of the biosensors, which could drive the shift "from lab to factory" and offer promising prospects for point-of-care testing (POCT) for emergency and serious illnesses.

2.3. Photoelectric chemical biosensors

As a new technology, photoelectric chemistry mainly studies the photoelectric conversion of photoelectric chemical (PEC) substances and its related applications[11]. Since the photoelectric effect was discovered by Becquerel in 1839, photochemistry has gained interest in photocatalysis as well as photovoltaics and PEC sensing tools over the past few decades. Recently, PEC sensing using light as an excitation source and current as an output signal has gained great popularity in detecting target markers due to advantages such as high sensitivity, easy miniaturization, and negligible background noise. Photoelectric chemical biosensors have the advantages of high sensitivity, high selectivity, real-time monitoring, etc., and are suitable for medical diagnosis, biomedical research, environmental monitoring, food safety and other fields. Juan Wang et al. reported a light-addressed and label-free PEC biosensor named LF-LAPECS for sensitive detection of multiple biomarkers on a single electrode. The key to LF-LAPECS is to manufacture semiconductor electrodes with high uniformity, stability, and conversion performance. In order to prepare nanocrystals Bi2S3 membrane modified ITO electrodes (Bi2S3/ITO) with the above properties, a two-step potentiostatic deposition method was proposed. The resulting Bi2S3/ITO with obvious homogeneity and strong conversion performance in the visible range is then modified by AuNPs and then separated into the same sensing region by an insulating coating. Adsorption stabilization of antibodies of 3 tumor biomarkers (e.g. AFP) on different sensing regions of the electrode and further blocking of BSA (Protocol 14). The method showed a detection limit as low as 5.0 pg/mL with a linear range of 0.01 to 1000 ng/mLfor AFP[12].

2.4. Surface-enhanced Raman spectroscopy

Raman spectroscopy was discovered by c.v. Raman in 1928, is a spectral analysis technique based on the Raman scattering effect, by adsorption or aggregation of molecules to be detected on the metal Surface nanostructures, using the metal surface Plasmon Resonance effect (Surface Plasmon Resonance, surface Plasmon resonance). The local electric field generated by the SPR enhances the Raman signal, thus significantly enhancing the Raman scattered signal of the sample and improving the sensitivity of the detection. With the advantages of high sensitivity, selectivity and real-time monitoring, SERS biosensor has been widely used in biomedicine, chemical research and food safety[13]. SERS is very suitable for the detection of AFP at low concentration. In 2017, Zhang et al. applied the evanescent wave theory to establish a new in situ immune study method for alpha-fetoprotein in untreated blood samples. For the first time, the in situ immunoassay of whole blood was realized. Under optimal conditions, the linear range of AFP detection in untreated blood is 50-500 ng/mL. In addition, dynamic studies of A-fetoprotein in PBS and untreated whole blood have shown that its diffusion coefficient is affected by its complex composition. The results of in situ and in vivo studies of A-fetoprotein in whole blood samples from Wistar rats represent the power of their novel pathway[14].

2.5. Other optical biosensors

The electrochemical luminescence (ECL) method is a special chemiluminescence technique that combines the principles of electrochemistry and luminescence. The method usually involves two substances, a luminescent substrate and a resonant energy transfer substance[15]. In the ECL process, when the resonant energy transfer substance is in an excited state, the energy is released through an electrochemical reaction with the electrode surface, thus stimulating the luminescent matrix to send out a light signal. This method combines the advantages of luminescence analysis and electrochemical analysis, and has the advantages of high sensitivity, simplicity, no background light signal, strong versatility, stability, fast, easy to control, etc., which has been widely praised in the development of ultra-sensitive biosensors for measuring biomarker detection. Zhang et al. developed an ECL immunoassay based on near hybridization method to detect protein expression of AFP and cancer cells. The sensor was prepared by self-assembly of ss-DNA3(partially hybridized by ss-DNA1 and ss-DNA2) and blocked on the Au electrode surface with 6 mercapto-1-hexanol (MCH). AFP binds to two SS-DNA-labeled antibodies (DNA1-Ab1 and DNA2-Ab2). Ru(phen) 32þ was embedded in ds-DNA and ECL measurements were made in

the presence of a reactant solution (Protocol 4). The linear range of AFP concentration was estimated to be 0.05e20.0 ng/mL, with a detection limit of 6.2 pg/mL. In addition, the method has been successfully used to detect A-fetoprotein overexpressed cancer cells with a detection limit of 620 cells /mL, and to identify A-fetoprotein expression on living cells[16].

The fluorescent biosensor is based on the specific interaction between the biometric element and the molecule to be detected, which causes the target molecule to bind or separate from the fluorescent marker, resulting in the change of fluorescence signal. Fluorescent biosensor has the characteristics of high sensitivity, real-time monitoring, high selectivity and non-destructive, and is widely used in biomedicine, environmental detection, food safety and other fields. Staining, labeling and sensing are three types of fluorescence technology Sensing technology is different from other types of fluorescence technology, it is an active rather than passive fluorescence signal transmission technology, according to the target, the fluorescence sensing platform can be "on" or "off", change the color and adjust the fluorescence [17]. Fluorescent biosensors are used to detect a large number of targets, both in solution and on membranes, as well as inside cells and in vivo. Et al show the preparation of ZnO nanowire by hydrothermal method in parallel microfluidic channels with different amounts of polyethylenimide (PEI) with microfluidic channels. As expected, the diameter of zno nanowire was reduced by the addition of PEI. The technique is more efficient than the convenience of hydrothermal techniques due to the effects of water-induced nutrient supplementation and shear stress. By attaching FITC-linked anti-bovine IgG (FITC-antiigg) to zinc oxide nanowires, fluorescence emission was significantly enhanced compared to the glass substrate and zinc oxide seed layer. The zinc oxide nanowire grown for 3 h under different growth conditions was enhanced by 5 mM PEI in solution, and the fluorescence enhancement was most significant. In addition, the optimized zinc oxide nanowires were assembled in a microfluidic channel to detect AFP respectively, and the detection limit was as low as 1 pg/mL. It can be seen that the wide dynamic range of AFP concentration is 6 orders of magnitude from 1pg /mL to 1mg /mL[18].

3. Conclusions

In this review, we explore the utilization of optical biosensors for the specific and super-selective determination of AFP. The integration of AFP with photonic biosensors offers the convenience of multiple operative tools. Compared to other methods, optical biosensor techniques have emerged as one of the most extensively used technologies due to their attributes of real-time monitoring, label-free detection, high specificity or sensitivity, minimal size, reduced reactants, expedited speed, cost-effectiveness, and simplicity. Despite the significant advancements in AFP detection using optical biosensing systems in recent years, several challenges necessitate further investigation. Firstly, the commercialization of optical biosensors is limited; thus, emphasis should be placed on the production of marketable biosensors. Prior to their clinical application, it is crucial to minimize environmental toxicity, enhance the utilization of visible light, and improve biocompatibility. Furthermore, the detection of AFP by optical biosensors remains a focal point of interest.

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