Application and Exploration of Biosensors for Cancer Liquid Biopsy and Artificial Intelligence-Assisted Data Analysis

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Abstract. Cancer is one of the diseases with the highest mortality rate in the world, and its early diagnosis and precise treatment have always been the focus of medical research. Traditional detection technology has limitations such as trauma and difficulty in dynamic monitoring, while biosensors combined with liquid biopsy as an emerging non-invasive detection technology can detect tumor-related markers in body fluids and convert them into quantifiable data through biosensors. However, liquid biopsy still faces challenges such as low marker concentration, weak signals, and complex data analysis. Therefore, it is necessary to combine high-sensitivity detection technology with intelligent data processing methods to improve its accuracy and clinical application value. This article will focus on the mechanism of biosensors in detecting tumor markers and the signal conversion process and provide a new path for cancer screening and detection with the assistance of artificial intelligence, which has a positive effect on breaking through the limitations of traditional detection methods.

1 Introduction

With the continuous development of precision medical equipment in the changing times, conventional cancer detection methods include PET-CT, MRI, pathological biopsy, endoscopy, and other invasive tests. In recent years, liquid biopsy is gradually been replacing conventional detection methods due to its non-invasiveness, high sensitivity, and real-time monitoring and control. At the same time, the access to artificial intelligence makes liquid biopsy technology faster and more accurate for data processing and model analysis, and it is likely to greatly affect almost all aspects of oncology, from enhanced diagnosis and personalized treatment to the discovery of new anti-cancer drugs [1]. However, its complex biological information and low marker content also bring great challenges to detection and data analysis. For this reason, combining signal amplification strategies and artificial intelligence technology has become a key path to breaking through bottlenecks.

Current research progress shows that Labib et al. systematically studied the mechanism of electrochemical biosensors for detecting small molecules, nucleic acids, and proteins in early cancer screening and developed a method for rapid, selective and highly sensitive

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analysis of clinically relevant molecules without the need for a pre-concentration step. Haiping Li et al. proposed a variety of signal amplification strategies such as enzyme-catalyzed signal amplification, nanomaterial signal amplification, and nucleic acid signal amplification to effectively reduce the detection limit. Minjung Kim et al. constructed a self-supervised algorithm to achieve automatic extraction of cfDNA methylation features and clinical data analysis, significantly improving the accuracy of early lung cancer screening and laying the foundation for the survival rate of cancer patients. Based on the previous work, this article will focus on the conduction mechanism of bioelectrochemical sensors and the assistance of artificial intelligence.

2 Structure and production mechanism of tumor markers

Oncogenes exist in human genes, and these genes can be detected as tumor markers. The increase in tumor markers is caused by changes in genetic and epigenetic levels during the mass replication of cancer cells. According to the genes that control the production of tumor markers, they can be divided into tumor suppressor genes (TSGs) and oncogenes (OGs). Oncogenes are suddenly activated due to the stimulation of cell growth and division, while tumor suppressor genes are usually inactivated when found in cancer. These genes are inactivated by loss-of-function (LoF) mutations (insertion/deletion and nonsense mutations), thereby preventing tumor suppressor genes from functioning in inhibiting cell proliferation, promoting DNA repair, and activating cell cycle checkpoints [2].

Tumor markers can be divided into protein markers, nucleic acid markers and tumor metabolism markers. Protein markers such as alpha-fetoprotein may be caused by incomplete differentiation of liver cancer cells, abnormal activation of AFP gene expression, liver tissue damage response, etc. Nucleic acid markers are DNA fragments released by tumor cells during apoptosis in the patient's body, which will be detected in the patient's blood (cfDNA and ctDNA and circulating tumor microthrombi CTMs). cfDNA is a common metabolite of normal cells and tumor cells, with a half-life of 1.5-2 hours. Detecting the half-life of metabolites can be used for early cancer screening [3]. Circulating tumor microthrombi are a mixture of platelets, white blood cells, cancer fibroblasts, etc. However, cfDNA is not a tumor-specific marker. High levels of cfDNA have also been found in patients with acute blunt trauma, burns, sepsis, and myocardial infarction (Rhodes A, et al 2006).

Therefore, it is particularly important to accurately distinguish and identify tumor markers. ctDNA is a DNA fragment unique to tumor markers, such as (TP53, EGFR, KRAS mutations), which can be detected by PCR and other technologies. However, due to the extremely low content of this DNA fragment in body fluids, the usual detection methods are not accurate and effective, and electrochemical sensors are required for detection. Tumor metabolic markers such as 2-hydroxyglutaric acid (2HG) and other metabolites have become potential markers for certain gliomas and leukemias. Due to the diversity and deformability of tumor metabolites, traditional detection methods will consume a lot of time and bring uncertainty to the patient's condition. Today, the advent of electrochemical sensors, due to their powerful data processing capabilities and the diversity of detection markers, has made it an important step forward in cancer research and patient survival rates.

3 Recognition and detection of tumor markers by electrochemical sensors

The main detection methods for liquid biopsy include digital PCR (dPCR), high-throughput sequencing (NGS), and immunosorbent assay (ELISA). Among them, electrochemical

biosensors are widely used in the detection of various tumor markers due to their high sensitivity and high selectivity.

The basic structure of a biosensor consists of three main parts: biorecognition elements, signal transducers, and data processing systems. Among them, the signal transducer is the core module for realizing the conductive mechanism, which is responsible for converting the biorecognition elements (such as antigens, antibody binding, nucleic acids, etc.) into electrical signals through changes in current and voltage [4]. With the development of liquid biopsy technology, the demand for highly sensitive detection of diversified and trace tumor markers is increasing. Electrochemical biosensors have attracted extensive attention in the early screening and auxiliary diagnosis of cancer due to their advantages of quantitative analysis, simple operation, rapid analysis, and low cost. Their core advantage is the ability to convert biomolecular recognition events into electrical signals, achieving visualization, high throughput, and real-time monitoring of trace biomarkers. A deep understanding of their conductive mechanism and signal amplification strategy is the key to improving their detection sensitivity and specificity and promoting their clinical application.

The key components of electrochemical sensors include working electrodes (usually made of gold, carbon, or glassy carbon materials), biorecognition elements (such as antibodies, DNA/RNA probes, enzymes, or specific tumor markers), electrolyte solutions, counter electrodes, and reference electrodes. The core of electrochemical sensors lies in the precise coupling mechanism between biorecognition events and electrochemical signals. When identifying tumor markers (such as AFP, ctDNA, miRNA), the process exhibits highly complex electrical signal response characteristics, it is mainly reflected in the changes in interface charge density, regulation of electric double layer capacitance, and nonlinear response of electrode reaction kinetics. When tumor marker molecules such as AFP bind to the biorecognition element on the sensor surface, it will cause changes in the electronic environment on the electrode surface, such as antigen-antibody binding or nucleic acid hybridization, which changes the charge distribution and changes the stability of the Electric Double Layer, or when the target molecule binds to the recognition element, it limits the transfer of electrons to the electrode and causes charge transfer resistance. Taking electrochemical impedance spectroscopy as an example, when the AFP concentration increases from 1 pg/mL to 100 ng/mL, the semicircle diameter in its Nyquist plot gradually increases, indicating that the charge transfer resistance increases from the original 128 Ω to 1875 Ω, showing a typical exponential response.

The electron transfer process of the electrode reaction can usually be described by the Butler-Volmer equation:

$$\mathrm{i} = \mathrm{i}_0 \left[\exp\left(\frac{\alpha \mathrm{nF}\eta}{\mathrm{RT}}\right) - \exp\left(\frac{-(1-\alpha)\mathrm{nF}\eta}{\mathrm{RT}}\right)\right] \quad (1)$$

i is the current density, i_0 is the alternating current density representing the electron transfer capacity under electrode equilibrium state, η is the overpotential, α is the electron transfer symmetry factor. During the marker binding process, the exchange current density i_0 decreases significantly, which is manifested as a decrease in the interfacial electron transfer rate, thereby causing phenomena such as a decrease in the peak current of the voltammetric characteristic curve (such as DPV) and a shift in the peak potential. For example, in a sensing system using an aptamer to recognize carcinoembryonic antigen, researchers observed that as the CEA concentration increased from 0.01 ng/mL to 100 ng/mL, the DPV peak current gradually decreased from 9.6 μA to 2.3 μA, and the peak potential also shifted significantly negatively, indicating that the binding event affected the electron injection behavior.

Since the content of target molecules (such as ctDNA, miRNA, proteins, etc.) in liquid biopsy samples is extremely low, often at the level of 10^{-15} M or even attomolar 10^{-18} M, it is necessary to use signal amplification strategies to improve the detection sensitivity of the

sensor. Signal amplification strategies include nanomaterial enhancement, electrocatalytic signal amplification, multiple signal output systems, etc.

3.1 Nanomaterial enhancement

Nanomaterials such as gold nanoparticles, graphene, and carbon nanotubes are often used to modify electrode surfaces due to their excellent conductivity and surface activity. These materials can significantly improve the electron transfer efficiency and the fixed capacity of target molecules, thereby amplifying the sensing response. For example, AuNPs-modified electrodes can achieve high-density antibody fixation through covalent bonding of thiol groups with antibodies and increase the electron transfer rate at the interface. In addition, graphene and its oxide (GO) have a large specific surface area and good electron migration performance, which can further enhance the sensitivity of electrodes and are suitable for the simultaneous detection of multiple tumor markers.

3.2 Electrocatalytic signal amplification

By introducing substances with catalytic activity (such as HRP horseradish peroxidase, Pt nanoparticles, red rhodium oxide, etc.), the substrate reaction can be catalyzed after the target binds to generate a strong electrical signal response. For example, after the AFP antibody binds to the electrode, a complex containing HRP is added. When AFP is present, an antigen-antibody complex is formed. The electronic reaction generated by HRP-catalyzed H_2O_2 can significantly amplify the current change and improve the detection sensitivity [5].

3.3 Multiple signal output system

In order to further improve the detection throughput and accuracy, some studies have adopted a multi-channel output strategy, that is, multiple signals such as current, voltage and impedance are monitored simultaneously to achieve cross-validation of results. For example, the biorecognition event simultaneously triggers current and fluorescence changes, and the analysis is performed in dual mode to improve the stability and credibility of the detection.

4 Artificial intelligence algorithms

The addition of artificial intelligence to liquid biopsy enables cancer to be detected and treated earlier. Compared with artificial intelligence testing, traditional testing may be biased by testers and require longer manual data analysis, which greatly affects the patient's condition judgment and treatment cycle. Multiple studies have shown that artificial intelligence technology has the potential to predict the diagnosis, prognosis and treatment response of certain malignant tumors (including colorectal cancer, breast cancer, skin cancer and lung cancer) [6]. The process of artificial intelligence detection of tumor markers is divided into obtaining raw signals from biosensors and preprocessing the data. When artificial intelligence detects high-frequency methylation, it includes noise filtering, normalization and missing value filling to ensure data consistency and accuracy. Next, through time domain and frequency domain feature extraction methods, combined with wavelet transform and Fourier analysis, the characteristics and location of tumor markers are quickly analyzed by calculating the mean, spectral characteristics, variance, and standard deviation, thereby generating a feature vector with high judgment ability. Subsequently, based on the characteristics of the feature, support vector machine (SVM), artificial neural network (ANN), CAD are used to train the judgment accuracy of the model.Through multiple

experiments, it has been shown that different models are better at detecting different cancers due to different algorithms. Some papers have confirmed the results that radiologists benefit the most from using CAD systems to detect prostate cancer lesions [7]. This is because the characteristics of prostate cancer are relatively stable, single, and repeatable. At the same time, technologies such as high-resolution MRI can capture subtle changes in these areas, thus providing CAD systems with clearer target areas. According to research, since large-model CAD systems are based only on enhanced dynamics and do not consider the morphology of lesions, inexperienced inspectors can also have more accurate judgments with the help of large AI models [8]. Octav G et al. used a support vector machine (SVM) classifier to screen the best candidate genes by using a colorectal cancer dataset from the Cancer Genome Atlas database as a reference. The authors reported that the accuracy of using SVM to classify and detect 40 colorectal cancer mutation genes reached 100%, which confirmed that the use of artificial intelligence assistance has further improved the accuracy of cancer detection [9, 10].

5 Conclusion

With the deepening of the concept of precise diagnosis and treatment of tumors, liquid biopsy technology is gradually becoming an important tool for early cancer screening and personalized treatment. This article systematically explains the structural characteristics and generation mechanism of tumor markers, analyzes the recognition principle, conductive mechanism, and signal amplification strategy of electrochemical sensors in liquid biopsy, and emphasizes the key role of nanomaterials, electrocatalytic reactions, and DNA nanostructures in improving detection sensitivity. At the same time, this article further explores the application potential of artificial intelligence in liquid biopsy data processing, including the auxiliary role of machine learning in tumor classification and mutation prediction, the ability of deep learning models to analyze complex omics data, and the advantages of self-supervised learning in feature extraction in unlabeled samples. Studies have shown that the deep integration of electrochemical biosensor technology and AI algorithms can effectively break through the bottlenecks of traditional detection methods in sensitivity, specificity, and data interpretation, thereby achieving earlier, more accurate, and more dynamic cancer monitoring. In the future, the coordinated development of liquid biopsy and AI technology will promote the evolution of tumor screening towards high-throughput, real-time, and wearable directions, and provide new technical paths and theoretical support for early detection, early diagnosis, and precise intervention of cancer, which has broad application prospects and far-reaching clinical significance.

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