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Recent Advances in the Application of Electrochemical Biosensors in Tumor Therapy

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Abstract: The progress in the application of electrochemical biosensors in tumor therapy aims to explore and study the latest developments and future trends of electrochemical biosensors in tumor therapy. This article first introduces the concept and classification of electrochemical biosensors, elaborates on the preparation methods and detection techniques of various electrochemical biosensors, and then reviews the application of electrochemical biosensors in tumor therapy. Finally, this article points out the research directions and challenges of electrochemical biosensors in improving sensitivity and specificity, expanding detection range and types, realizing multiplex detection and integration, and achieving portability and intelligence.

Keywords: Electrochemical Biosensor; Tumor; Therapy.

1. Introduction

Tumor therapy is an important research direction in the medical field, and electrochemical biosensors, as a new type of biomedical technology, have a wide range of application prospects in tumor therapy. Electrochemical biosensors are biosensors that use electrochemical methods to convert the biological recognition reaction of tumor cells into measurable electrical signals. Depending on the biological recognition elements, electrochemical biosensors can be divided into electrochemical immunosensors (using antibodies or other affinity proteins to bind with tumor antigens), electrochemical gene sensors (using probe DNA to hybridize or catalyze with tumor-related genes), and electrochemical drug sensors (using enzymes or other catalysts to react with tumor-related drugs).

2. Concept of Electrochemical Biosensors

Electrochemical biosensors are designed to have high sensitivity and specificity by combining specific tumor cell surface markers with nanomaterials or biochips. These biosensors can quickly and accurately detect tumor cells, providing strong support for doctors' diagnosis and treatment.

3. Classification of Electrochemical

Biosensors In tumor therapy, electrochemical biosensors, as a new type of therapy, have been widely applied in clinical practice. Among them, electrochemical immunosensors can identify and detect tumor cells through specific antibodies, and at the same time destroy the cell membrane and cytoskeleton of tumor cells through electrochemical reactions, thereby killing tumor cells. Electrochemical gene sensors can realize early diagnosis and treatment of tumors by detecting the gene expression level of tumor cells. In addition, electrochemical drug sensors can improve the therapeutic effect of drugs and reduce side effects by directly delivering drugs to the tumor site.

3.1. Electrochemical Immunosensors

Electrochemical immunosensors are biosensors that use electrochemical impedance spectroscopy technology combined with antibodies or other affinity proteins as biological recognition elements. Electrochemical immunosensors can be classified according to electrode type, substrate material, composition, and functionalization method, and can detect different types of bacteria, viruses, fungi, and disease markers. Electrochemical immunosensors do not require labeling and do not depend on specific enzymes. Instead, they rely on the specific binding between the biological recognition element and the analyte to cause changes in the capacitance and charge transfer impedance on the electrode surface.

Here are some common types of electrochemical immunosensors:

3.1.1. Disposable Biosensor based on CNT

This sensor can detect EGFR as low as 2 fg/mL, which improves the LOD compared to commercial kits at that time. Another biosensor for EFGR detection is to deposit AuNPs on the electrode, which achieved LODs of 0.34 pg/mL and 0.88 pg/mL in PBS and human plasma samples respectively [1].

3.1.2. Impedance Immunosensor Based on Gold Microelectrodes

This sensor is used to detect and quantify prostate-specific antigen (PSA), a biomarker overexpressed in prostate cancer. This sensor achieves an LOD at the ng/mL level[2]. Another impedance immunosensor used to detect ovarian cancer serum marker cancer antigen 125 (CA-125) functionalizes gold nanoparticles wrapped with silica gel and quantum dots on a gold electrode platform[3]. This system can detect CA-125 in ovarian cancer patient serum in less than an hour with an LOD of 0.0016 U/mL[3].

3.1.3. Impedance Immunosensor Based on Glassy Carbon Electrode Platform

This sensor is used to detect brain tumor marker MDM2, pediatric adrenal cortical carcinoma (pACC) marker DHEAS, Mycobacterium tuberculosis, infection indicators CD14 and CD16 monocytes[4]. These sensors all use AuNPs or other nanostructures to enhance sensitivity and specificity.

3.1.4. Impedance Immunosensor based on Novel Protein Scaffolds

In addition to antibodies, there are some novel protein scaffolds such as nanobodies, Affimers etc., that can serve as biological recognition elements. These protein scaffolds have advantages such as high stability, low cost, easy preparation etc. Impedance immunosensors based on these protein scaffolds have been successfully applied to detect testosterone, rabbit IgG, Her4 protein tumors etc.

3.2. Electrochemical Gene Sensors

Electrochemical gene sensors are biosensors that use electrochemical methods to detect and quantify target DNA molecules. The core of electrochemical gene sensors is to fix specific probe DNA on the electrode surface and undergo hybridization or catalytic reactions with target DNA, thereby changing the electrochemical properties of the electrode.

According to the interaction mode between probe DNA and target DNA, electrochemical gene sensors can be divided into several types:

3.2.1. Hybridization-type Electrochemical Gene Sensor

This sensor uses complementary hybridization between probe DNA and target DNA for recognition. The hybridization reaction will cause changes in charge, mass, structure etc., on the electrode surface, thereby affecting parameters such as electrochemical impedance, potential, current etc., of the electrode. This sensor can amplify and convert signals in a labeled or label-free manner[5]. For example, a hybridization-type electrochemical gene sensor based on gold nanoparticle labeling can detect tumor-related gene p53 as low as 1 fM [5].

3.2.2. Catalytic-type Electrochemical Gene Sensor

This sensor uses catalytic reactions between probe DNA and target DNA for recognition. The catalytic reaction will produce some oxidizable or reducible products, thereby changing the oxidation-reduction reaction rate and current intensity on the electrode surface. This sensor usually needs to add some catalysts or enzymes to promote the reaction[6]. For example, a catalytic-type electrochemical gene sensor based on the CRISPR/Cas9 system can detect target DNA as low as 10 aM and distinguish mutation sites[6].

3.2.3. Molecular Switch-Type Electrochemical Gene Sensor

This sensor uses conformational changes between probe DNA and target DNA for recognition. The conformational change will cause changes in the conductivity or redox activity on the electrode surface, thereby affecting parameters such as resistance, capacitance, charge transfer etc., of the electrode. This sensor usually needs to design some special structure probe DNAs, such as hairpin-type, triple helix-type, double helix-type etc[7]. For example, a molecular switch-type electrochemical gene sensor composed of hairpin-type probe DNA and silver nanowires can detect hepatitis B virus DNA as low as 0.1 pM and distinguish different subtypes[7].

3.3. Electrochemical Enzyme Sensors

3.3.1. Principle of Electrochemical Enzyme Sensors

Electrochemical enzyme sensors are biosensors that use enzymes as biological recognition elements to catalyze the oxidation or reduction reactions of target substrates, thereby producing detectable electrons or redox intermediates[8].

3.3.2. Consists of Electrochemical Enzyme Sensors

Electrochemical enzyme sensors usually consist of three parts: working electrode, reference electrode and auxiliary electrode. The working electrode is the core of the sensor, responsible for fixing the enzyme on the surface and reacting with the target substrate. The reference electrode is used to maintain a constant potential difference, and the auxiliary electrode is used to provide a current loop[9].

3.3.3. Types of Electrochemical Enzyme Sensors

Electrochemical enzyme sensors can be divided into two types according to the signal conversion method: direct type and indirect type. The direct type sensor refers to the enzyme-catalyzed reaction directly producing oxidizable or reducible substances, such as oxygen, hydrogen peroxide, NADH etc., these substances can undergo redox reactions on the working electrode, producing a current signal proportional to the substrate concentration. The indirect type sensor refers to the enzyme-catalyzed reaction indirectly affecting the redox reaction on the working electrode, such as changing the pH of the solution, ion strength, oxygen content etc., these changes will cause changes in parameters such as impedance, potential, capacitance etc., on the working electrode, thereby producing a signal related to substrate concentration[10].

4. Progress in the Application of Electrochemical Biosensors in Tumor Therapy

4.1. Electrochemical Immunosensors

The following is the progress in the application of electrochemical immunosensors in tumor therapy:

4.1.1. Detection of Tumor Markers

Electrochemical immunosensors can utilize antibodies or other affinity proteins to specifically bind with tumor markers, thereby achieving rapid, sensitive, and accurate detection of tumor markers. Tumor markers are proteins or other molecules that are overexpressed or secreted in tumor cells, such as prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2) etc. Electrochemical immunosensors can detect tumor markers in body fluids such as blood, urine, saliva etc., thereby achieving early diagnosis of tumors, prognosis assessment and monitoring of treatment effects[11].

4.1.2. Capture and Analysis of Tumor Cells

Electrochemical immunosensors can also utilize antibodies or other affinity proteins to bind with specific receptors on the surface of tumor cells for capture and analysis of tumor cells. Tumor cells refer to malignant cells that have fallen off from primary lesions and entered into blood circulation, such as circulating tumor cells (CTC), circulating tumor micro clusters (CTM) etc. Electrochemical immunosensors can detect tumor cells in blood to reflect tumor metastasis ability and treatment response[12].

4.1.3. Evaluation and Regulation of Immunotherapy

Electrochemical immunosensors can also utilize antibodies or other affinity proteins to specifically bind with immune-related molecules for evaluation and regulation of immunotherapy. Immunotherapy is a treatment method that uses the body's own immune system to recognize and eliminate tumor cells, such as immune checkpoint inhibitors, monoclonal antibodies, cancer vaccines etc. Electrochemical immunosensors can detect immune-related molecules in blood such as cytokines, chemokines, immunoglobulins etc., thereby evaluating patient's immune status and treatment effects[13].

4.2. Electrochemical Gene Sensors

The following is progress in application of electrochemical gene sensors in tumor therapy:

4.2.1. Detection of Tumor-Related Genes

Electrochemical gene sensors can utilize specific probe DNA fixed on the electrode surface to hybridize or catalyze reactions with target DNA, thereby achieving rapid, sensitive, and accurate detection of tumor-related genes. Tumor-related genes are some genes that are abnormally expressed or mutated in tumor cells, such as p53, KRAS, EGFR, HER2 etc. Electrochemical gene sensors can detect tumor-related genes in body fluids such as blood, urine, saliva etc., thereby achieving early diagnosis of tumors, molecular typing and personalized treatment[14].

4.2.2. Monitoring of Tumor Microenvironment

Electrochemical gene sensors can also utilize specific probe DNA fixed on the electrode surface to hybridize or catalyze reactions with target miRNA or lncRNA, thereby achieving monitoring of the tumor microenvironment. The tumor microenvironment refers to the cellular and molecular composition around tumor cells, including immune cells, vascular cells, fibroblasts, extracellular matrix etc. The tumor microenvironment is closely related to the occurrence, development, metastasis and drug resistance of tumors. miRNA and lncRNA are some non-coding RNAs that regulate gene expression. They play an important role in the tumor microenvironment. Electrochemical gene sensors can detect miRNA and lncRNA in tumor tissues or body fluids to reflect the state and changes of the tumor microenvironment[15].

4.2.3. Evaluation and Regulation of Gene Therapy

Electrochemical gene sensors can also utilize specific probe DNA fixed on the electrode surface to hybridize or catalyze reactions with target siRNA or CRISPR/Cas9, thereby achieving evaluation and regulation of gene therapy. Gene therapy is a treatment method that uses exogenous genes to repair or replace abnormal genes, such as siRNA-mediated silencing, CRISPR/Cas9-mediated editing etc. Electrochemical gene sensors can detect siRNA or CRISPR/Cas9 in tumor cells or body fluids to evaluate the effect and safety of gene therapy [16].

4.3. Electrochemical Enzyme Sensors

The following is progress in application of electrochemical enzyme sensors in tumor therapy:

4.3.1. Detection of Tumor Metabolites

Electrochemical enzyme sensors can utilize enzymes as biological recognition elements to catalyze oxidation or reduction reactions of target metabolites, thereby producing detectable electrons or redox intermediates. Tumor metabolites are some molecules that are abnormally produced or consumed in tumor cells, such as lactic acid, pyruvic acid, glucose etc. Electrochemical enzyme sensors can detect tumor metabolites in body fluids such as blood, urine, respiratory gas etc., thereby achieving early diagnosis of tumors, metabolic status assessment and monitoring of treatment effects[14].

4.3.2. Detection of Tumor-Related Enzymes

Electrochemical enzyme sensors can also utilize antibodies or other affinity proteins to specifically bind with target enzymes for rapid, sensitive and accurate detection of tumor-related enzymes. Tumor-related enzymes are some enzymes that are abnormally expressed or activated in tumor cells, such as ubiquitin hydrolase (USP7), histone deacetylase (HDAC), ubiquitin ligase (E3 ligase) etc. Electrochemical enzyme sensors can detect tumor-related enzymes in tumor tissues or body fluids to reflect the occurrence, development, metastasis and drug resistance of tumors[17].

4.3.3. Evaluation and Regulation of Gene Therapy

Electrochemical enzyme sensors can also utilize specific probe DNA fixed on the electrode surface to hybridize or catalyze reactions with target siRNA or CRISPR/Cas9 for evaluation and regulation of gene therapy. Gene therapy is a treatment method that uses exogenous genes to repair or replace abnormal genes, such as siRNA-mediated silencing, CRISPR/Cas9-mediated editing etc. Electrochemical enzyme sensors can detect siRNA or CRISPR/Cas9 in tumor cells or body fluids to evaluate the effect and safety of gene therapy[13].

5. Future Development Directions of Electrochemical Biosensors in Tumor Therapy

The future development directions of electrochemical biosensors in tumor therapy include the following aspects:

5.1. Improving Sensitivity and Specificity

The sensitivity and specificity of electrochemical biosensors are key factors affecting their detection performance. To improve sensitivity and specificity, various strategies can be adopted, such as optimizing the selection and fixation methods of biological recognition elements, designing new signal amplification and conversion mechanisms, and introducing nanomaterials and biomolecular markers[17].

5.2. Expanding Detection Range and Types

Electrochemical biosensors are currently mainly used for detecting tumor markers, tumor-related genes, and the tumor microenvironment. To more comprehensively assess the status and treatment effect of tumors, more types of electrochemical biosensors can be developed, such as detecting extracellular vesicles of tumor cells, tumor stem cells, tumor immune cells etc [18].

5.3. Realizing Multiplex Detection and Integration

Most electrochemical biosensors currently are single or dual detection, and cannot simultaneously detect multiple tumor-related molecules. To improve detection efficiency and accuracy, multiplex detection and integrated electrochemical biosensors can be developed, such as using different electrodes, signals or channels to achieve multiplex detection, or integrating electrochemical biosensors with other technologies such as optics, acoustics, microfluidics etc[14].

5.4. Realizing Portability and Intelligence

Most electrochemical biosensors currently require professional instruments and personnel for operation and analysis, which cannot meet the demand for on-site rapid detection. To improve detection convenience and reliability, portable and intelligent electrochemical biosensors can be developed, such as using paper-based or flexible substrates to prepare cheap, disposable, bendable electrochemical biosensors, or using wireless communication or cloud

computing technology to achieve remote control and data processing[19].

6. Result and Discussion

Through literature review, we find that electrochemical biosensors have broad application prospects in tumor therapy. Specifically, electrochemical immunosensors, with their high specificity and sensitivity, can effectively detect and kill tumor cells. Electrochemical gene sensors can facilitate early diagnosis and treatment of tumors, but there is a need for further improvements in their stability and reliability. Electrochemical enzyme sensors can enhance the therapeutic effect of drugs and reduce side effects, but further research is needed to understand their mechanisms of action and clinical outcomes.

In addition, we find that the application effectiveness of electrochemical biosensors is influenced by various factors such as sensor preparation methods, detection techniques, and mechanisms of action. Therefore, there is a need to further enhance sensitivity and specificity, expand the detection range and types, research and optimize the preparation methods and detection techniques of electrochemical biosensors to achieve multiplex detection and integration, realize portability and intelligence, and achieve precise control and evaluation of their performance. At the same time, in-depth research on the mechanisms of action and clinical effects of electrochemical biosensors is needed to promote their widespread application in tumor therapy.

7. Conclusion

This review mainly explores the progress in the application of electrochemical biosensors in tumor therapy. Through literature review, we find that electrochemical biosensors have a wide range of application prospects in tumor therapy, but there are still some problems and challenges. In the future, it is necessary to further research and optimize the preparation methods and detection techniques of electrochemical biosensors, deeply explore their mechanisms of action and clinical effects, to promote their widespread application and development in tumor therapy.6.14，6.22

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