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Electrochemical Biosensors: Principles, Clinical Applications, Challenges and Future Perspectives

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Abstract. With the growing demand for fast, sensitive and inexpensive detection methods, the development of electrochemical biosensors has accelerated in clinical diagnosis, environmental monitoring, and food safety. Traditional analysis methods tend to be costly, complicated, and very expensive to perform, making them restricted to use at the point of care and in real time detection. Hence, this paper attempts to explore the principles, performance, and latest advancement of electrochemical biosensors as a promising substitute to traditional analytical techniques. It examines how biological recognition elements (enzymes, antibodies, nucleic acids) are combined with electrochemical transducers to convert specific biological events into measurable electrical signals. Previous research on sensor design and modification, electrode, and nanomaterials and signal amplification strategies were analyzed using a review research approach. It was found that there are major advancements in the area of nanomaterials and electrode surface engineering that have greatly increased sensitivity, selectivity and limits of detection. Electrochemical biosensors also had other beneficial traits such as quick responsiveness, lower cost, small size and they could be integrated into portable devices. In general, electrochemical biosensors have a lot of potential in future point-of-care diagnostics and personalized treatment but further technological advances are needed so that it can be reliably applied on large scale.

Keywords: electrochemical biosensor, electrochemical sensing, clinical diagnosis, biomarker detection, point-of-care diagnostics

1. Introduction

The development of modern medicine has increased the demand for rapid and precise detecting methods of disease-related substances. Current diagnostic techniques, such as laboratory immunodetections, polymerase chain reaction (PCR) and chromatography, can guarantee high accuracy, but they often require expensive instruments, professional personnel and a long testing time. These shortcomings are particularly obvious in the on-site testing where quick responses and portable devices are necessary. Consequently, biosensors have attracted increasing attention as a new analytical tool in bioanalysis [1, 2].

An electrochemical biosensor is a device which combines a biological detecting instrument with an electrochemical transducer. The recognition element can specifically bind to the target analyte,

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and the transducer transforms the biological reaction into an electrical signal. According to the detection method, the signal may differ in current, potential, conductivity or impedance [3]. The main advantage of the electrochemical biosensor is to directly change biological information into an electrical output.

Electrochemical biosensors have been employed in the determination of metabolites, proteins, nucleic acids, antigens, antibodies, pathogens and cancer markers [4, 5]. For example, glucose sensors are used for diabetes monitoring. Recently, nanomaterials, microfluidics, wearable instruments and mobile phone based systems have extended the use of electrochemical biosensors [6, 7].

Furthermore, there exists a significant discrepancy between the excellent analytical results obtained in laboratory experiments and the reliable use in clinics. Some newly designed sensors show very small detection levels under ideal experimental conditions, but their efficiency may be reduced in actual blood, serum, saliva or sweat due to interferences and biofouling. Therefore, this paper discusses the fundamental principles, clinical utility and major limitations of electrochemical biosensors, and explores potential strategies to facilitate their clinical translation.

2. Electrochemical biosensors

A biosensor is an analytical instrument that detects a target analyte via a biological recognition element and converts this recognition event into a measurable signal. In electrochemical biosensors, the transforming device is based on an electrochemical reaction. The recognition element may comprise enzymes, antibodies, nucleic acids, aptamers, or other biological biomolecules [3, 8].

The main composition of an electrochemical biosensor generally includes three essential parts: a biorecognition agent, an electrode/transducer and a signal processing system. The biorecognition agent possesses the property of selectivity. For instance, glucose oxidase can specifically combine with glucose, whereas an antibody can recognize a certain antigen. After the recognition process, the electrode detects the alteration of the electrochemical conditions and gives out an electrical signal.

The electrode is very important since the biological event usually happens near its surface. Therefore, the properties of electrode materials and their surface structures exert a significant influence on the sensor's sensitivity and stability. The common electrode materials are gold, platinum, carbon, graphene and other conductive materials [3, 9].

The general working process can be described as:

Target analyte → biological identification → modification at electrode surface → electrochemical response → electrical indication

In the sensor which contains an enzyme, the target molecule reacts with the enzyme. This biochemical reaction alters the concentration of electroactive species or modulates the electron-transfer process at the electrode surface. Therefore, the electrode transforms this change into an electrical signal. For instance, in an amperometric sensor, the produced current is proportional to the target substance concentration [4] .

There are several major types of electrochemical detection.

Amperometric biosensors measure the current resulting from an electrochemical oxidation or reduction process. The current is generally related to the concentration of the target substance. This technique is mainly used in enzyme-type sensors, particularly in glucose sensors [4].

For example, glucose oxidase catalyzes glucose oxidation. The resulting products are electrochemically detectable, and the current varies with glucose concentration. This technique is easy to operate and suitable for miniaturized electronic devices.

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Some sensors can detect small changes in electrical potential which are related to the activities or concentrations of certain ions or charged particles. This technique is applicable for the determination of ions and some biochemical substances.

Voltammetric methods determine the current when the potential of the applied electrode is altered. Various techniques such as cyclic voltammetry and differential pulse voltammetry can give insight into the oxidation and reduction processes. These methods are especially suitable for achieving high sensitivity.

Electrochemical impedance spectroscopy (EIS) is used to detect variations in the impedance of an electrode system. When an antigen attaches to an antibody which is immobilized on the electrode surface, the interfacial properties may be affected. These changes might result in a modification of the electron-transfer resistance detected by EIS. Consequently, the concentration of the target substance can be calculated from the impedance change [3, 10].

This principle is particularly beneficial for immunosensors since the antigen-antibody binding does not always result in an electroactive substance. Rather, the binding process alters the electrode surface.

3. Clinical applications of electrochemical biosensors

Electrochemical biosensors have been investigated for different clinical applications like metabolic disorders, cancer, cardiovascular diseases and infectious diseases. Their key clinical advantage is the ability to deliver rapid results using small biological samples.

3.1. Glucose monitoring

Glucose determination is a crucial clinical use of electrochemical biosensors. Diabetic patients need to monitor their blood glucose frequency, but the present laboratory tests are unsuitable for continuous observation.

Glucose biosensors usually contain glucose oxidase or glucose dehydrogenase as the biological recognizing element. The enzymatic reaction causes an electrochemical change which can be detected by the electrode. The improvement of electrochemical glucose sensors has also promoted the continuous glucose monitoring (CGM) systems. These systems employ a miniaturized sensor to obtain glucose-related information continuously or repeatedly and afterwards send the data to an electronic instrument.

The application of glucose sensors indicates the advantage of electrochemical biosensors that can change complex biological information into a simple electrical signal. The present sensor systems can be linked to wireless communication and digital health networks.

3.2. Cancer biomarker detection

Cancer diagnosis is also an important field. Various cancers are associated with changes in the concentrations of specific proteins, nucleic acids, and other biomarkers. Electrochemical immunoassay can detect these biomarkers through the use of antibodies and transform the binding reaction into an electrical signal.

For instance, prostate specific antigen (PSA) has been widely researched as a marker connected with prostate diseases. Electrochemical immunosensors can immobilize antibodies on the electrode surface and detect the changes caused by the binding of antigen and antibody. The same methods

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have also been examined for other biomarkers such as carcinoembryonic antigen (CEA) and cancer-related proteins

The primary advantage is that electrochemical detection can achieve ultra-low limits of detection with small sample volumes. Graphene and metal nanoparticles are usually employed to enlarge the electrode surface area and accelerate electron transfer, which may improve the analytical sensitivity.

High sensitivity cannot guarantee the clinical significance of a sensor. The cancer biomarkers might be present in very small amounts and there are other proteins and substances in the biological materials. Hence, both selectivity and excellent performance in actual samples are equally important.

3.3. Cardiovascular disease biomarker detection

Electrochemical biosensors have been studied for the identification of cardiac disease markers. Cardiac troponins are important for recognizing myocardial injury. An early diagnosis might be advantageous in urgent and field situations.

Recent investigations have tried to improve the sensitivity of electrochemical sensors by employing nanomaterials, enzyme-free techniques and various electrode structures. However, clinical validation is required for the detection of cardiovascular biomarkers, because the sensor must be able to distinguish the significant concentration changes from the background interference in complex biological fluids [11].

Therefore, future development of electrochemical biosensors for cardiovascular biomarkers should consider not only lowering the limits of detection. In addition, reproducibility, selectivity, sample preparation and standardised clinical testing are also important.

3.4. Infectious disease detection

Electrochemical biosensors can distinguish not only pathogens but also their related markers. Different kinds of recognition substances like antibodies, aptamers, DNA probes etc., can be used to discriminate between bacteria, viruses or particular nucleic acid sequences [12].

When compared with the conventional laboratory-based method for pathogen detection, electrochemical systems might provide quicker results and be more convenient for integration into portable instruments. This feature is especially desirable for point-of-care diagnosis, where quick decisions are needed.

Furthermore, it is technically difficult to detect pathogens since clinical specimens often include several disturbing components. Moreover, some detection methods need preparatory or amplification procedures. Hence, reducing the entire detection procedure is an important area of research.

Over all, compared with some usual analytical methods, electrochemical biosensors have several advantages. They are generally small, inexpensive, quick and applicable for portable devices. Only a little number of electronic components are required to measure electrical signals. These characteristics make them suitable for on-site inspections and for health surveillance.

4. Limitations of electrochemical biosensors

Blood, serum, saliva and sweat contain different proteins, ions, metabolites and other substances. Some of them may influence the electrochemical signal. Hence, a sensor that functions properly in typical laboratory media may yield variable results in real biological samples.

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This problem is particularly serious when the target analyte is at a low concentration. A interfering substance may result in a similar electrochemical response and reduce the detection accuracy.

Biofouling occurs when proteins and other types of biological materials attach to the sensor surface in an improper way. It may obstruct the electrode and influence the electron transfer process. Therefore, the sensor signal might decrease or change during its use.

This problem is of special significance for wearable and implantable sensors which require long-term use in biological environments. Therefore, antifouling surface coatings and advanced electrode materials are the fields of study [6, 13].

Biological recognition elements such as enzymes and antibodies may lose their activity over time.. Their performance is affected by environmental conditions like temperature and pH. Also, the differences in electrode fabrication and surface processing cause variations in the sensors.

This is an important issue in commercialization. A sensor should give stable outcomes not only in its initial use but also in various batches and different devices.

One of the main issues is the difference between the results of laboratory experiments and their actual use in clinics. Most of the academic investigations concentrate on parameters like the detection limit, sensitivity and linear range. Nevertheless, the clinical devices also have to meet the needs concerning precision, strength, production, user manipulation, durability and regulatory confirmation.

A recent study indicates that the good analytical ability of electrochemical biosensors has not been fully utilized in the market because of the challenges in constructing large-scale and reliable systems [14]. Therefore, more research is needed to concentrate on clinically significant samples and standardization of validation.

5. Discussion

The progress of electrochemical biosensors has evolved from basic enzyme-type sensors to more complicated systems including nanomaterials, microfluidics, wearable instruments and digital technologies. This advancement has greatly enhanced the utilization of electrochemical biosensing.

Nanomaterials are highly valuable because they can increase the active surface area of electrodes and facilitate electron transfer. For instance, graphene has been considered mainly due to its conductivity and large surface area. Other nanomaterials can also exhibit catalytic activity or improve the bonding of biological recognition substances.

Nevertheless, nanomaterials cannot be applied only to achieve a very low detection limit. The usefulness of a material lies in its ability to be produced uniformly, maintain stability during usage and work efficiently in actual samples. Presently, more and more research indicates that clinical application needs to consider the balance among analytical performance, stability, producibility and system integration [14, 15].

Another significant field is the combination of electrochemical biosensors with wearable and portable devices. They can measure biomarkers in sweat, interstitial fluid, saliva or other types of biological fluids and send the results to mobile phones or computers. This might modify the conventional sensing method into a continuous health surveillance.

Artificial intelligence and machine learning may also be useful. The data obtained from wearable sensors is generally difficult to handle by hand. Machine-learning approaches can be applied to find patterns, reduce interference and improve signal understanding. Nevertheless, these methods require dependable and uniform data.

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Thus, the progress of electrochemical biosensors in the future should not be based solely on their sensitivity. A practical biosensor for clinical use must be able to give trustworthy and medically significant outcomes under actual patient circumstances. This needs the combination of electrochemistry, biology, material science, engineering, medicine and data science.

6. Conclusion

Electrochemical biosensors are promising analytical techniques which combine biological detection with electrochemical signal transformation. They possess the features of rapid reaction, high sensitivity, reasonable expense, small instrument size and are appropriate for portable and wearable instruments. These properties make them suitable for medical applications such as glucose measurement, cancer biomarker detection, cardiovascular disease diagnosis and infectious disease diagnostics.

Some difficulties still remain. The influence of biological substances, biofouling, the variability of biological recognition substances, low repeatability and difficulty in large-scale manufacture might influence the practical effectiveness. Primarily, there is a gap between outstanding experimental outcomes and trustworthy clinical instruments.

Additional investigation is required not only to improve the detection capabilities. Attention should be paid to real clinical samples, stability under long-term usage, repeatability in production, anti-fouling methods, standardization of testing and the combination with portable and wearable equipments.

Furthermore, electrochemical biosensors may play a significant role in the future of point-of-care and personalized healthcare. Nevertheless, their successful establishment will rely not only on technological advancement, but also on demonstrating that these instruments can give consistent, precise and clinically relevant outcomes under actual circumstances.

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