Int. J. Electrochem. Sci., 17 **(2022)** Article Number: 22104, doi: 10.20964/2022.10.26

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Mini Review

Recent Development of Electrochemical Immunoassay for Determination of Liver Cancer Biomarker Carcinoembryonic Antigen

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Received: 2 May 2022 / *Accepted:* 30 May 2022 / *Published:* 10 September 2022

Carcinoembryonic antigen (CEA) is a series of biomarkers for cancer diagnosis. It can be used with other specific bioindicators for the early diagnosis of lung cancer and postoperative cancer metastasis identification. Therefore, it is necessary to establish a highly sensitive and rapid detection technique. The electrochemical immunoassay technique combines the specificity of immunoreactivity and the rapidity of electrochemical techniques, making it a promising detection technique in clinical practice. This review summarizes the development process of electrochemical immunosensors in CEA detection. Different types of electrochemical immunosensors and their advantages and disadvantages are explored. Also, a series of representative works are listed. We also discuss the role played by different nanomaterials in sensor construction. Finally, we discuss the future trends on this topic.

Keywords: Carcinoembryonic antigen; Electrochemical immunoassay; Cancer cell metastasis; Biosensor; Rapid Test; Graphene

1. INTRODUCTION

The Global Oncology Epidemiology Statistics data show that lung cancer's incidence and mortality rate increase and are highest among malignant tumours. The pathological types of lung cancer include small cell lung cancer and non-small cell lung cancer. Although small cell lung cancer accounts for only 15%-20%, it is poorly differentiated, has a short ploidy time, has the highest malignancy, and has a poor prognosis [1–3]. How to prolong the survival of small cell lung cancer patients has always

been a hot and challenging topic. The current diagnosis of lung cancer mainly depends on pathology and imaging examinations. Therefore, the diagnosis rate is not high in the early stage. Tumour marker testing has limitations due to the polyphenism of lung cancer cells, while combined testing of multiple markers is tedious [4–7]. However, the emergence of protein microarray technology in recent years has brought hope to solving these challenges. Therefore, screening suitable lung cancer tumour markers for early diagnostic microarrays is crucial [8].

Tumour markers refer to chemicals produced by tumours that can reflect the presence of the tumour itself. They are produced, secreted by tumour cells and released directly into cellular tissue components during carcinogenesis and proliferation [9,10]. They are often present as antigens, enzymes, hormones or metabolites within tumour cells or in host body fluids. These substances are not present in normal adult tissues or are only found in embryonic tissues. In another group of cases, their levels in tumour tissue greatly exceed those in normal tissue. Their presence or quantitative changes can reflect the nature of the tumour, tumour histogenesis, cell differentiation, and cell function [11,12]. Tumour markers have high sensitivity and specificity, which help in the early diagnosis, determining pathological types and cancer staging, assessing treatment effects and prognosis, and guiding individualized treatment [13,14].

Lung cancer metastasis is the underlying cause of poor prognosis for many patients. This is a widespread clinical problem in treating lung cancer with local and distant metastases [15,16]. A significant number of lung cancer patients die from complications related to metastasis. Therefore, it is crucial to evaluate lung cancer metastasis factors accurately. As a common location of metastasis, the lymph nodes determine the stage and prognosis of lung cancer. Several studies have detected multiple factors related to lymph node metastasis [17,18]. The detection of lymph node metastasis using molecular biology is mainly divided into the following two categories: (1) detection of protein-based markers specific to the tissue of origin of lung cancer (2) detection of lung cancer-specific genetic alterations, which can be detected in lymph nodes or blood that do not contain such substances and make a prediction [19].

Carcinoembryonic antigen (CEA) is a class of glycoproteins secreted by gastrointestinal cells and was one of the first broad-spectrum tumour markers discovered [20–22]. It mediates interepithelial cell adhesion as homophilic adhesion that is not dependent on calcium ions, and CEA can also be elevated in the serum of lung cancer patients. Early studies have shown higher serum CEA concentrations in healthy smokers than non-smokers. The literature reports typical serum CEA values of 2.5 ng/mL-6.9 ng/mL [23]. The majority of studies have a positive value of 5 ng/mL. CEA elevations due to benign disease are usually less than 10 ng/mL. Elevated serum CEA concentrations can help in the diagnosis. Elevation of CEA alone is not diagnostic for non-small cell lung cancer because CEA is elevated in other malignancies. Detection of both CEA and CYFRA21-1 is more meaningful for predicting non-small cell lung cancer. Detection of all CEA, SCC-Ag and CYFRA21-1 is highly sensitive for diagnosing and evaluating non-small cell lung cancer [24]. In peripheral blood from non-small cell lung cancer tested for CEAmRNA, positive results were found in patients with mediastinal lymph node metastases. At the same time, no mRNA was detected in those without metastases. This represents a relationship between its detection rate and lung cancer stage and lymph node metastasis,

which can be used to indicate lung cancer metastasis [25]. Therefore, how to efficiently and rapidly detect CEA has been an important topic in analytical chemistry.

This represents a relationship between its detection rate and lung cancer stage and lymph node metastasis, which can be used to indicate lung cancer metastasis. Therefore, how to efficiently and rapidly detect CEA has been an essential topic in analytical chemistry [26]. Researchers have explored mainly detection methods, nanocomposites, various biochemical sensors, and diverse options for biomaterials [27–29]. Currently, many promising research results have been obtained for carcinoembryonic antigen detection. The detection methods include fluorescence immunoassay, piezoelectric immunoassay, chemiluminescence immunoassay, surface plasmon resonance, electrochemical immunoassay, etc.

2. ELECTROCHEMICAL IMMUNOASSAY

Combining empathetic sensing technology with individual immune responses, biosensors that monitor antigen-antibody reactions are called immunosensors. The concept of immunosensor was introduced by Henry et al. in 1990 [30]. Because of the advantages of high analytical sensitivity, high specificity, ease of use and low cost, immunosensor technology has been involved in a wide range of fields such as clinical medicine and bioassay technology, food industry, environmental monitoring and treatment. The electrochemical immunosensor is one of the earliest studies, most diverse and more mature branches of immunosensors. Votalmmetric techniques can significantly enhance the sensitivity of the immunosensors [31–38]. Related research has opened up a wide variety of research and application areas over the decades and is now moving toward greater sensitivity, efficiency, miniaturization, and applicability [39]. Electrochemical immunosensors can be divided into non-labelled and labelled types according to whether or not a marker is used in the immunoassay process. Electrochemical immunosensors are mainly conductivity, impedance, and current types depending on the measurement signal [40,41].

Conductivity-based immunosensors achieve detection by changing the conductivity of the semiconductor on the sensor mainly through an immune response. As shown in Figure 1, devices made of semiconductor Si wires are used for quantitative detection and analysis by causing changes in the conductance of the semiconductor material after the occurrence of immune-binding proteins.

Figure 1. Scheme of immunoassay by conductance immunosensor.

Impedance-based immunosensors are a sensing technique based on the measurement of resistance in the equivalent loop of an oscillator. This method has been developed in recent years because it does not require other reagents or separation means to determine the electrochemical properties of the immunoassay system and does not cause any harm to the system. For example, Chen et al. [42] prepared an impedance-based immunosensor via a gold membrane immobilized with antibodies. They achieved high accurate sensing of C-reactive protein via inhibiting the electroactivity of the $Fe(CN)_6^{3-/4-}$ through the formation of immune complexes. Li et al. [43] prepared a three-dimensionally ordered polyaniline macroporous membrane permeated with ionic liquid by an electropolymerization method, which was combined with the assembly of gold nanoparticles to prepare a novel HBsAg impedance immunosensor. Zhou et al. [44] developed an impedance-based immunoassay using carbon nanotubes (CNTs)-AuNPs nanocomplexes to immobilize antibodies. They achieved electrochemical determination of glycoprotein CA19-9 by inhibition of the electrochemical behaviour of the $Fe(CN)_6^{3-/4-}$ probe by a silica nanosphere marker bound to the electrode surface by sandwich immunoreaction.

In 1979, Aizawa [45] first reported an amperometric immunosensor to detect human chorionic gonadotropin (HCG). In contrast to other bioassays, antigen-antibody binding in immunosensing is accompanied by only small physicochemical changes. Therefore, most amperometric immunosensing methods for the determination of immunoconjugate reactions are usually expressed by other auxiliary reactions. It is common practice to amplify the assay by labelling one of the immunoreactions using some molecule that can be easily measured. Amperometric immunosensor measurements generally involve two steps: first, an enzyme marker is bound to the sensor surface by a competitive or sandwich-type immunoreaction [46,47]. The cleaning step removes substances that are not explicitly bound to the sensor surface, eliminating the effect of non-specific adsorption. The immune response is monitored by the current signal generated by the beacon molecule for quantitative detection. Compared with other electrochemical immunosensors, amperometric electrochemical immunosensors have been widely studied and applied in recent years because they are more convenient to operate and have higher sensitivity [48].

Electrochemiluminescence (ECL) is a process in which a redox reaction occurs on the surface of an electrode, causing light emission. The most commonly used in ECL labelling is ($[Ru(bpy)_3]^{2+}$). When the oxidizing type reacts with a suitable reducing agent, its light can be measured. Sardesai et al. [49] recently reported the sensitive detection of two analytes in 1 × 1 inch pyrolytic graphite sheets with SWCNT microarray ECL.

3. ELECTROCHEMICAL IMMUNOSENSOR FOR CEA DETECTION

The current trend indicates that different nanomaterials can assist analyte recognition, increase analyte-binding and signal amplification, and enable ultra-sensitive and selective detection [50–52]. Additionally, collaborations in nanotechnology and bioelectronics have shown new avenues for scaling down and fabricating extremely sensitive immunosensors via nanomaterials. The most crucial elements to consider when developing and constructing electrochemical immunosensors are the stable loading of antibodies and signal magnification [53]. Numerous nanomaterials have been utilized to enhance

electrochemical signals and thereby increase the sensitivity of electrochemical immunosensors due to different inherent properties [54,55]. Specifically, different types of nanomaterials such as noble metal nanoparticles, carbon nanomaterial, and composites have been used to construct immunosensors for CEA detection.

Nanocomposite materials composed of biopolymers and organic and inorganic nanoparticles are a critical area of study in contemporary material science [56]. It blends the physicochemical properties of individual components to create innovative composite materials with enhanced properties [57]. Nanoparticles and nanomaterials display distinct chemical, physical, and electrical characteristics that distinguish them from their bulk counterparts, making them attractive for biosensor applications [58–63]. AuNPs are the most widely employed metal NPs owing to their innovative biocompatibility, high surface area, and electrical characteristics [64–66]. Compared to single metal NPs, bimetal NPs exhibit unique properties, with one metal exhibiting long-term stability and biocompatibility and the other exhibiting the desired optical or electrical activity [67]. The majority of publications on bimetallic NPs concern the combination of Au with another metal, such as Ag, Pd, Ru, or Pt. Carbon materials are suitable electrodes for electroanalytical chemistry due to their favourable characteristics. Among them, single-walled carbon nanotubes (SWCNT) have been employed to create biosensors. SWNTs significantly increase the surface area of the electrode in electrochemical experiments owing to their high aspect ratio [68,69]. Additionally to their high conductivity network structure, SWCNT can act as a bridge between biomolecules and immunosensor, resulting in a high sensitivity [70]. Chitosan (CS) is a polysaccharide formed when chitin is deacetylated. Due to its outstanding membrane-forming capacity, water permeability, strong adhesion, biocompatibility, and mechanical strength, CS has been extensively employed as an immobilization matrix for fabrication [71].

Graphene can be directly used to immobilize cAb through a covalent bond, but it is often combined with AuNPs, polymers, and other molecules to promote immobilization performance. AuNPs have been synthesized using a well-established wet chemical reduction method using hydrogen tetrachloroaurate(III) trihydrate as a precursor. Additionally, the surfactant has been introduced during the reduction for regulating the size of AuNPs [72]. Alternatively, electrochemical deposition of AuNPs on the gold [73] or GC [74] surface is another quick and straightforward method of increasing the active surface area. Applied voltage, precursor concentration and deposition time can regulate the size and density of AuNPs. The electrochemical immunosensors for CEA determination that have been recently described are mentioned in Table 1. For instance, Lan et al. [75] developed a new label-free electrochemical CEA immunosensor based on reduced graphene oxide@polystyrene/PtNPs. Due to its high biological compatibility and wide specific surface area, the composite is advantageous for streptavidin immobilization and subsequent loading of biotinylated CEA antibodies. After the introduction of CEA, the generated nonconductive immune composites may inhibit the electron transaction of $[Fe(CN)_6]^{3-/4-}$ probes, and therefore the resulting current response corresponding to the CEA concentration. Jozghorban et al. [64] demonstrated the development of a simple label-free electrochemical immunosensor to detect CEA. First, the GC electrode was partly coated with rGO to provide a substrate for antibody binding. The antibody was used to coat the electrode surface with rGO using EDC/NHS as a linker. The electrochemical behavior of the electrode was then examined utilizing CV and EIS. The current or impedance changes can reflect the CEA concentration. The proposed sensor

demonstrated a satisfactory amperometric response to CEA with a 0.05 ng/mL detection limit across the concentration range of 0.1–5 ng/mL. Additionally, the new technique was examined to detect CEA in human blood serum, and the findings were shown to be equivalent to the ELISA reference values.

Table 1. Sensing performance of recently published electrochemical immunosensors for CEA detection.

Sensor interface	Linear detection range	LOD	Reference
AuNP–graphene/ HRP-anti-CEA Ab	0.010–10 ng/mL	0.04 ng/mL	[76]
AuNPs/graphene/ cAb/HRP-dAb	0.10–80 ng/mL	0.04 ng/mL	[77]
MoS_2-PBNCs/HRP-anti-CEA Ab	0.005–10 ng/mL	0.00054 ng/mL	[78]
AuNPs/BSNa-CNC-PPy/HRP-anti-CEA Ab	0.001 pg/mL–200 ng/mL	0.06 fg/mL	[79]
AuNPs/CNOs/SWCNTs/CS/HRP-anti-CEA Ab	0.1 pg/mL–400 ng/mL	0.1 pg/mL	[80]
AuNPs/thionine/rGO/anti-CEA Ab	10–500 pg/mL	4 pg/mL	[81]
AuNPs/anti-CEA/graphene	0.5–120 ng/mL	0.17 ng/mL	[82]
AuNPs/PB/anti-CEA Ab/HRP-anti-CEA Ab/AuNP–graphene s	0.05–350 ng/mL	0.01 ng/mL	[83]
anti-CEA Ab/rGO/chitosan/AuNP/MCF	0.05 pg/mL-1 ng/mL	0.024 pg/mL	[84]
AuNPs/PB-PEDOT/anti-CEA Ab	50 pg/mL–40 ng/mL	10 pg/mL	[85]

Due to the inherent limitations of immune proteins as redox indicators in immunoassays, secondary antibodies and signal amplifiers have been widely used to monitor the current intensities of electroactive probes in most immunosensors [86,87]. Consequently, it is critical to design effective label materials with superior catalytic properties for sensitive immunosensing systems [88–90]. To begin, Cu^{2+}-Au@Pt dendritic nanomaterials functionalized with N-doped graphene with enormous surface areas and outstanding adsorption capacities were synthesized and used as label to capture multiple secondary antibodies [91].

The immunosensor's electrochemical reaction to the target marker corresponds the electroactive response after developing an immunocomplex. This structure can be used to simultaneously determine the CEA with other cancer biomarkers. Recently, a few unlabeled investigations were undertaken. Lin's group, for example [92], studied the electrochemical detection of CEA in clinical serum samples using DPV. In this regard, an immunoelectrode was constructed using an ITO with the loading of AuNPs and MPSi. Methylene blue and 6-(ferrocenyl) hexanethiol were used for MPSi surface functionalization and subsequently used as labels for reflecting the changes of the electrode status. The labels were captured using PVA as a binding agent on the ITO electrode surface. DPV was used to identify the target cancer

antigens after non-labelled contact. Consequently, CEA had linear ranges of 0.5–50 ng/mL with a limit of detection of 0.1 ng/mL.

Silica has been the most widely used nanomaterial for modification processes due to its chemical inactivity, which prevents aggregation, and the abundance of surface hydroxyl functional groups that readily connect to organic functional groups. In a nutshell, SiO_2 acts as a coating layer [93]. Lin and colleagues [94] developed an ITO platform modified with MPSi for the electrochemical detection of CEA in this context. To begin, nanostructures of ferrocenecarboxylic acid and horseradish peroxidase were created. After immobilization of the CP-Abs onto the electrode surface, anti-CEA@FcC@MPSi was formed. Following the Ab-Ag reaction, the target antigens were quantified using DPV. The CEA can be linearly detected between 0.5–45 ng/mL with a limit of detection of 0.2 ng/mL.

Kong et al. [95] created a branching sensor for the simultaneous sensing of dual cancer antigens non-labelled and reagentless. To demonstrate the feasibility of this design, they constructed an ITO branching electrode system for loading two antigens. To generate a different voltammetric current capable of discriminating between two antigens, C-GRS@MB and C-GRS@PB were synthesized. Following that, the antibodies were immobilized on C-GRS@MB and C-GRS@PB, respectively. Each of these electroactive molecules was loaded independently on the branching electrode. Following an unlabeled immunoreaction, target antigens were quantified using DPV in the ranges between 0.5–80 ng/mL. The limit of detection can be calculated to be 0.05 ng/mL.

Photoelectrochemical (PEC) measurement is a recently established and promising analytical approach for biological tests [96], has gained considerable attention and rapid growth in measurement [97]. Light illumination is used to excite the photoactive species in PEC detection, and the photocurrent is used as the detection signal. Due to the utterly distinct energy forms have a shallow background signal and a very high sensitivity. Additionally, using an electronic readout simplifies and lowers the cost of the equipment compared to other optical detection systems [98]. Thus, PEC detection is an intriguing method for detecting CEA.

Photoactive material is the most important part of a PEC immunosensor. TiO_2 is an ideal material for the fabrication of PEC immunoassays due to its electrochemical activity [97], cheap cost, and high electron transfer rate [99]. Nonetheless, TiO_2's large bandgap precludes its use in visible light [100]. Two alternative materials may be used to address this issue. CdSe with a small bandgap of 2.1 eV, has been intensively investigated in PEC sensing [101,102]. $BiVO_4$, a non-toxic semiconductor with a bandgap of 2.4 eV, has garnered considerable interest owing to its unique properties, including non-toxicity, cheap cost, ease of fabrication, adequate mobility, and a comparatively long minority carrier diffusion length [103,104].

Compared to a single-sensitized structure, a multiple-sensitized or co-sensitized structure may make the most use of available light energy and significantly improve photovoltaic conversion efficiency [105]. A CEA sensor was fabricated based on CdSe@$BiVO_4$ composite assisted TiO_2 [106]. TiO_2 has a vast surface area and high biocompatibility, providing an abundance of antibody capture locations. The immunosensor was then sequentially loaded with CEA and signal antibodies labelled with CdSe@$BiVO_4$. Effective energy level matching between TiO_2, CdSe, and $BiVO_4$ maximizes light utilization and increases charge separation, hence improving PEC performance.

4. CONCLUSION

In summary, this review summarizes advances in electrochemical immunoassay sensors to detect CEA, which is an indicator of many cancers and therefore highly sensitive detection is of great clinical importance. Electrochemical immunosensors have the potential to be used as highly sensitive and rapid biosensors for clinical detection. The clinical application of electrochemical immunosensors faces a number of challenges. For example, the stability of immunoassays is strongly dependent on the external environment. How to improve the robustness of the sensor is an issue that needs to be addressed. On the other hand, the assembly of electrochemical immunosensors requires a tedious process, and these steps need to be simplified again to meet the needs of clinical use.

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