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Mini Review

Electrochemical Biosensors for COVID-19

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Abstract

Today COVID-19 pandemic caused by the SARS-CoV-2 virus is the most challenging health issue due to the fast transmission rate and its impact on different aspects of human life. Although RT-PCR is the primary method to detect SARS-CoV-2, other reliable methods are being developed to detect this pathogen. Biosensors can provide fast, reliable, and point-of-care diagnostic. Among them, electrochemical biosensors attract considerable interest. In this mini-review, I will summarize few electrochemical biosensors which have been developed to detect the SARS-CoV-2 virus.

Keywords: COVID-19; SARS-CoV-2; Electrochemical method; Biosensor

Introduction

SARS-CoV-2 belongs to coronavirus families which are responsible for respiratory, hepatic, enteric, and neurological diseases. Coronavirus name originated from the Latin word coronam (crown) because of the crown-like image of this type of viruses on the electron microscope image [1]. People affected by COVID-19 show symptoms like fever, nonproductive cough, shortness of breath, myalgia, fatigue, anosmia, ageusia, normal or decreased leukocyte count and ground-glass opacities [2].

Biosensors based on the transducer can be categorized into electrochemical, optical, mechanical and thermal devices. Among biosensors, electrochemical biosensors are extensively applied owing to simple operation, high sensitivity and applicability in turbid and colored solution as well as capability of use in the portable device [3,4]. The International Union of Pure and Applied Chemistry (IUPAC) define electrochemical biosensors as “a self-contained integrated device which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is retained in direct spatial contact with an electrochemical transduction element”. Bioreceptors which can apply in biosensor are DNA probes, aptamer, antibody, enzymes, tissues and cell reporters [5,6]. These biomolecules are the key players as they can provide the selectivity of the biosensor. Most electrochemical biosensors developed for COVID-19 are based on antibody and one paper studied the applicability of DNA probes. In this review, the method for fabrication of the device, selectivity and sensitivity of sensors are also discussed.

Electrochemical Biosensor

Electrochemical biosensors measure changes in resistance, capacitance, potential and current due to biological binding events at the biosensor surface [7]. Various types of electrochemical biosensors including potentiometric, voltammetric, and impedimetric as well as field-effect transistors are applied to detect different analytes.

Voltammetric biosensor

In voltammetric biosensors, the interaction between analyte and bioreceptor is detected by changing current as a function of applied potential. The square wave voltammetry method was applied to detect SARS-CoV-2 virus antigen. The purposed biosensor was fabricated by drop-casting carbon nanofiber on the surface of a screen-printed carbon electrode followed by electrografting of carboxyphenyl groups through the reduction of a diazonium salt. Then the Nucleocapsid (N) protein antigen was covalently bond to the electrode surface via EDC/NHS chemistry. The detection zone was covered with a piece of cotton fiber to collect a nasal sample directly on the electrode surface. The immunosensor was immersed into a PCR tube to record measurements. In this system binding positively charged antibody with antigen on the electrode surface led to an increase in reduction peak current of the redox probe (Ferro/Ferricyanide). For detection of a protein antigen, a fixed concentration of N protein antibody was mixed with different concentrations of N protein antigen. The complex was incubated on the electrode surface. The higher the concentration of antigen in the solution, the smaller the amount of antibody remained in the solution. Therefore, there was a smaller reduction in the reduction peak current. The percentage increase in the peak current of the redox probe showed a linear relationship with the logarithmic concentration of antigen in the range of 1 to 1000 ng/mL of the N protein. The aforementioned immunosensor sensor was shown to present a low detection limit and good selectivity toward other virus antigens like Flu A or HCoV and was demonstrated in the detection of antigen in nasopharyngeal swabs sample [8].

Potentiometric biosensor

Potentiometric measurements are based on measuring the potential difference between two electrodes which are separated by a prem-selective membrane by means of a high-impedance potential measuring device. The two electrodes can be an indicator or reference electrode or two reference electrodes [6,9]. An immuno-potentiometric sensor based on SpikeS1 antibody of SARS-CoV-2 electro-inserted to kidney cells membrane was developed to detect SARS-CoV-2 antigen. The suspension of membrane engineered cell/antigen s1was produced with several steps and added to the wells of the polydimethylsiloxane layer. These wells were located on eight gold screen-printed electrodes. Interactions of electro-inserted SARS-CoV-2 antibody and SARS-CoV-2 spike protein in the solution resulted in changing potential of membrane-engineered cells which was measured by the multichannel potentiometer. The potentiometer device is connected to a tablet to measure real-time changes in the

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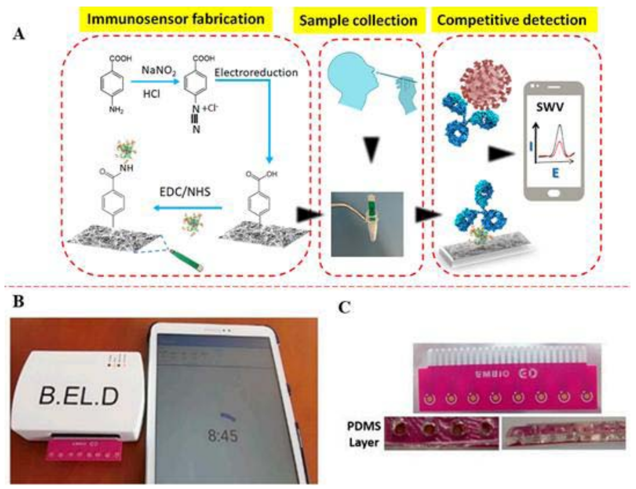

Figure 1: A) Voltammetric immunosensor left to right electrografting of the electrode surface, sample collection and competitive mechanism with permission ref [8]. B) The potentiometric device and disposable sensor with permission ref [10].

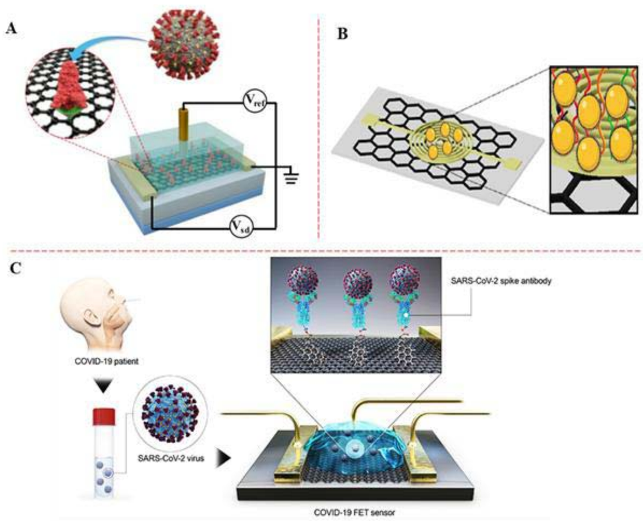

Figure 2: A,C) Schematic of graphene field effect transistor with permission ref [12,13]; B) Schematic configuration of the electrochemical chip with gold nanoparticle with permission ref [14].

electric properties of the cells. The purposed biosensor showed a detection limit of $1fgmL^{-1}$ and a linear range of response between $10fg^{-1}\mu gmL^{-1}$. The potentiometric device and disposable sensor strip were showed in Figure 1B and 1C respectively [10].

Field effect transistor

In a field effect transistor, the electroconductivity of the semiconductor channel between two electrodes (source and drain) is controlled by a gate electrode. Attachment of charged biomolecules to the bioreceptor resulted in threshold voltage variations that change the current in the channel [11]. Graphene FET biosensor modified electrostatically either with SARS-CoV-2 spike S1 subunit protein (CSAb) or angiotensin-converting enzyme 2 ACE2 were developed to identify COVID-19 spike protein S1. CSAb demonstrated higher affinity in affinity measurements. The biosensor work principle was based on variation in conductance/resistance (filed effect) due to attachment of spike protein with a slightly positive charge on the modified graphene surface. The fabricated immunosensor can obtain LOD 0.2pM [12]. The Schematic of this graphene field effect transistor was shown in Figure 2A. An aqueous solution-gated FET biosensor in which the changes in channel surface potential is the basis of the detection developed to detect SARS-CoV-2. The graphene channel was modified with SARS-CoV-2 spike antibody via 1-Pyrene Butyric Acid N-hydroxysuccinimide Ester (PBASE) linker. The purposed biosensor was showed excellent selectivity toward MERS-CoV protein and applicable in detecting SARS-CoV-2 nasopharyngeal swabs and cultured SARS-CoV-2 virus [13]. The Schematic of the purposed field effect transistor was illustrated in Figure 2B.

Electrochemical chip

An electrochemical biosensor coupled with an electrical readout setup was utilized to detect nucleocapsid phosphoprotein (N-gene) of SARS-CoV-2. For the fabrication of the sensor, the filter paper was modified with graphene solution. The predefined gold electrode was deposited on the graphene layer. The system utilized four antisense oligonucleotides (ssDNA) capped on gold nanoparticles for two separate regions of the N-gene. Hybridization between RNA of virus and ssDNA resulted in the change in charge and electron mobility on the graphene surface which causes the change in sensor voltage. The senor showed good sensitivity toward MERS-CoV or SARS-CoV RNA and applicable in Nasopharyngeal swab specimens to detect viral COVID-19 RNA [14]. The Schematic of this DNA sensor was demonstrated in Figure 2C. The above-mentioned biosensors are summarized in Table 1.

Conclusion

In this mini-review, few electrochemical biosensors and their application in the detection of COVID-19 covered. The purposed biosensor can obtain an excellent detection limit and showed good selectivity toward other viruses. As infectious diseases are a potential threat for human being and the environment, there is still the need for

Table 1: Electrochemical biosensor for detection of COVID-19.

Method	Biomolecules	LOD	Linear Range	Ref
Square wave voltammetry	Nucleocapsid (N) protein antigen	$0.8pgml^{-1}$	1 to 1000 $ngmL^{-1}$	[8]
Potentiometry	SpikeS1 antibody of SARS-CoV-2	$1fgmL^{-1}$	$10fg^{-1}\mu g\ mL^{-1}$	[10]
Field effect transistor	SARS-CoV-2 spike S1 subunit protein	LOD 0.2pM.	-	[12]
Field effect transistor	SARS-CoV-2 spike antibody	$1fgmL^{-1}$. Culture medium (limit of detection $1.6\times10^{1}pfumL^{-1}$ & clinical samples 2.42×10^{2} Copies mL^{-1}	$1fgmL^{-1}$ PBS and $100fgmL^{-1}$ clinical transport medium	[13]
Electrochemical chip	Nucleocapsid phospho-protein (N-gene) of SARS-CoV-2	6.9 copies μL^{-1}	585.4 copies μL^{-1} to 5.854×10^{7} copies μL^{-1}	[14]

developing new biosensor which can apply in the field measurement. In addition, various real samples should investigate with the purposed biosensors to evaluate the accuracy and precision of these devices. It is expected that novel biosensors with different bioreceptor will introduce in the future. Moreover, a comparison between these devices from different aspects like sensitivity, selectivity, reliability with the conventional methods should provide in ongoing research.

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