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Clinical utility of novel biosensing platform: Diagnosis of coronavirus SARS-CoV-2 at point of care

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ABSTRACT

Early detection is the first step in the fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Therefore, an efficient, rapid, selective, specific, and inexpensive SARS-CoV-2 diagnostic method is the need of the hour. The reverse transcription-polymerase chain reaction (RT-PCR) technology is massively utilized to detect infection with SARS-CoV-2. However, scientists continue to strive to create enhanced technology while continually developing nanomaterial-enabled biosensing methods that can provide new methodologies, potentially fulfilling the present demand for rapid and early identification of coronavirus disease 2019 (COVID-19) patients. Our review presents a summary of the recent diagnosis of SARS-CoV-2 of COVID-19 pandemic and nanomaterial-available biosensing methods. Although limited research on nanomaterials-based nanosensors has been published, allowing for biosensing approaches for diagnosing SARS-CoV-2, this study highlights nanomaterials that provide an enhanced biosensing strategy and potential processes that lead to COVID-19 diagnosis.

1. Introduction

Diagnostics developed using, for example, conventional immunological tests such as radioimmune assay and enzyme-linked immunosorbent assay detect levels of special viral immunoglobulins in serum patients [1]. At the same time, other methods are based on the detection of nucleic acids (DNA or RNA) in aa quantitative and qualitative manner [2] and are amplified using polymerase chain reaction technology (PCR) [3], the critical development of a point-of-care diagnostic assay for disease detection, monitoring, and management. Such point-of-care includes tests that analyze samples in field hospitals, outside clinical laboratory settings, and are often performed by clinical staff without laboratory training for quick results, and such systems are based on lateral flow immunoassays [4–6]. Viral isolation is the gold standard procedure and the most sensitive approach, even though it takes 3–7 days and is tedious [7]. Anyway, the serological examinations of viral antibodies against viral antigens are less sensitive and non-specific [8]. Nanosensors are quantitative procedures employed to identify numerous infectious illnesses in straightforward, real-time, and effective methods [9]. The design of glucose oxidase biosensors reported by Clark and Lyon was one of the earliest biosensor reports at the beginning of the sixties [10]. Biosensors consist of bioreceptor, transducers, and signal processing systems as three primary parts [11]. Bioreceptor in biosensors may selectively interact with the biomarker utilizing monoclonal antibodies, glycans, nucleic acid, lectin, enzyme, tissue, or entire cells, as depicted in Fig. 1 [12]. The transducer converts these interactions to a quantifiable and measurable signal and then analyses and reports qualitative and quantitative pathogen identification using obtained signals [13,14]. The target analyte comprises antigenic viruses, which might be the entire virion, virus capsid proteins, virus-specific antibodies, and viral nucleic acids.

Biosensors have been prepared and functionalized using

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nanoparticles to improve the specificity and selectivity of the detection of target molecules. The available sensing platforms have been developed over the past few decades. The immobilization of the solid phase transducers (carbon, gold, silicone, or hydrogels) onto a conducting polymer surface (polyaniline or polypyrrole) alternatively covalent conjugation through linkers to form self-assembled monolayers with a terminal functional group (thiol, carboxyl, amine, and maleimide) that binds to the transducer surface. The selective binding between the analyte with the sensing platforms leads to biochemical signals, including pH, electron flow, mass, and heat changes. These generated changes can be converted and amplified to generate a measurable signal (optical and electrochemical biosensors). A general biosensor relies on optical exposure of analytes such as surface plasmon resonance (SPR) and surface-enhanced Raman scattering (SERS) [15,16]. Such optical sensing platforms depend on direct and indirect detection techniques. Indirect binding through the fluorophores as tagging and labeling methods, the direct methods depend on the refraction of the analyte with optical properties and measure the changes in the refractive index at the interface as measured by SPR based sensors allow for real-time monitoring. Nanomaterials such as silver NPs (AgNPs), gold (AuNPs), carbon-based are commonly used with optical sensing [17]. The photon strikes the metallic surface of the NPs at a precise angle. This is followed by light energy pairs with the electrons of the metallic surface, leading to excitation due to electrons movement as in the SPR example [18,19].

One of the significant challenges for the development of biosensor platforms is to design appropriate biological sensors for screening or diagnostics, and it is necessary to determine the clinical infectious dosage of SARS-CoV-2. Most viral RNA samples in higher respiratory tract concentrations are between $10^2$ and $10^8$ copies per swab, and the highest is 7.11 copies per dab at the first week of the start of the symptoms and, in most cases, more than $10^2$ per dab at the first week in sputum and stool dose [20]. As indicated by a recently completed virological laboratory analysis of 9 patients, most viruses in the RNA samples are more than $10^2$ copies per dab [20].

For example, the use of ultrasensitive graphene field-effect transistor immunosensor has been described in recent times as an effort to easily and rapidly screening for SARS-CoV-2 [21]. The SARS-CoV-2-spike S1 subunit antibody protein (ACE2) or the angiotensin-converting (2) receptor has been conjugated to a graphene surface. The hybridization of the S1 protein receptor-binding domain (RBD) with the immobilized spike S1 subunit protein antibody/ACE2 receptors, which could be read electrically in a mild form, changes its conducting/resistance via the field effect [22]. This immune-based biosensor can instantly recognize the SARS-CoV-2 spike S1 at 0.2 pM, instantaneously and without being labeled, and accurately bind to it. The graphene-coated surface with SARS-CoV-2 antibodies generated measurable electrical changes that can be directly correlated with the viral presence from samples obtained via saliva swabs or serum. This approach was reported from 19 patient’s data and reported to be sensitive with a load of detection that reached $2.42 \times 10^2$ copies/mL [23]. Such an approach holds great potential in minimizing false positive detections, giving the complexity of biological samples used to detect the virus. One possible approach to developing a SARS-CoV-2 biosensor is using non-structural surface glycoproteins ORF8 and E2 that may bind and release the heme...
porphyrin inside the 1-beta hemoglobin chain. SARS-CoV-2 proteins attach to hemoglobin molecules of the transducer that releases a hemoglobin portion that generates an electric signal when considered for heme concentration measurement before and after the examination. Alternatively, the anti-spike RBD monoclonal antibodies of Human-IgG1 bind directly with the analyte spike protein [12]. A lateral flow test for detecting immunoglobulins that can distinguish between COVID-19 patients within 15 min and identify the infection stage by detecting IgG or IgM for precise and rapid viral detection.

Another approach following the metagenomic RNA sequencing method was utilized to distinguish the SARS-CoV-2 genome shortly after the preliminary occurrence was reported based on next-generation sequencing. However, this technique is sensitive and is limited by performance, turn-around time, expenditure, and high technological capability needs. During pulmonary dysfunctions caused by SARS-CoV-2 infections, traces of mitochondrial reactive oxygen species (ROS) have been overproduced. Therefore, a reliable and straightforward ROS sensor has been developed using this phenomenon for a sample isolated from 500 µl patients' sputum samples [24]. The electrochemical immunosensor comprises carbon nanotubes coated on a steel needle’s tip with three electrodes resembling electrochemical cells (work, counter, and reference). The observations have been obtained under sweeping potential from −0.8 to 0.8 V with a scan rate of 100 mV/s. The reported result showed that over 97% of the actual positive patient test were detected using this ROS system in 30 s [25].

During this pandemic, the need to develop reliable and fast detection methods was in high demand. Hence the development of paper-based biosensors as a cheaper alternative, biodegradable, and the ease to fabricate makes them one of the suitable alternative detection methods [26]. Lateral flow test strips, for example, were used to identify SARS-CoV-2. It is intended to detect IgG and IgM in patient serum, blood, or plasma samples [27]. Thus every test strip typically comprises of (i) sample pad for the test samples; (ii) a SARS-CoV-2 antigen, conjugated to gold-SARS-CoV-2; and the gold-rabbit IgG; (iii) IgG-coated control line with an IgG test line with an anti-human IgG-coating and IgM test line with an anti-human IgM [28]. Once IgM and/or IgG are present in patient samples, antibodies react to form a complex containing gold-SARS-CoV-2 antigen migrating over the nitrocellulose membrane, interacting on their respective test lines with anti-IGMs and/or IgGs. In turn, the gold-rabbit IgG reacts to the visible red color utilizing the anti-rabbit IgG coated at the control line. A positive IgM or negative IgG or positive suggests a primary or acute infection in both directions, but a positive IgM denotes a secondary or later stage of infection with negative IgM [29]. The glass fiber for viral nucleic acid detection, loop-mediated isothermal amplification is another rapid technology analytic strip (LAMP), and integrated lateral flow test strip to generate a detectable colorimetric signal [30].

Nevertheless, compared to the primary detecting method, such an essential instrument requires a heat block for amplification. Each functional layer is separated by hydrophobic polyvinylchloride substrate, which control the fluid flow between layers. To substantially simplify processes, a simple, automated, feasible, and integrated paper-based biosensor has been built [17].

2. Conclusions

Following the shocking numbers of casualties and the catastrophic economic crisis globally, rapid advances have been made to fight against coronavirus disease 2019 (COVID-19). Improved and accurate methods are essential in this context to avoid and control any potential future viral or microbial outbreaks. Thus, laboratory-independent, high-throughput and reliable, inexpensive, and portable screening is the most crucial technology to be developed. Along with considerations of extraordinary responsiveness, minimal size, and low costs, new sensors based on well-designed nanomaterials, nanotechnology, and innovative sensing processes have the potential to develop next-generation biosensors. Advances in molecular and synthetic biotechnology, the finding and bioengineering of new coupling materials such as nanobodies and aptamers can make it easier to identify new pathogens in the future. New intelligent sensing techniques combine biosensors’ incredible sensitivity with improvements in artificial intelligence and various technologies that can improve control over the spread of pathogens. In summary, developing nano-based biosensors with such appealing features can provide the opportunity for rapidly screening for viral infection within a population and contribute toward confining viral spread.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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