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EDITORIAL

Role of miRNA-21 in cancer and its application in electrochemical bioanalysis

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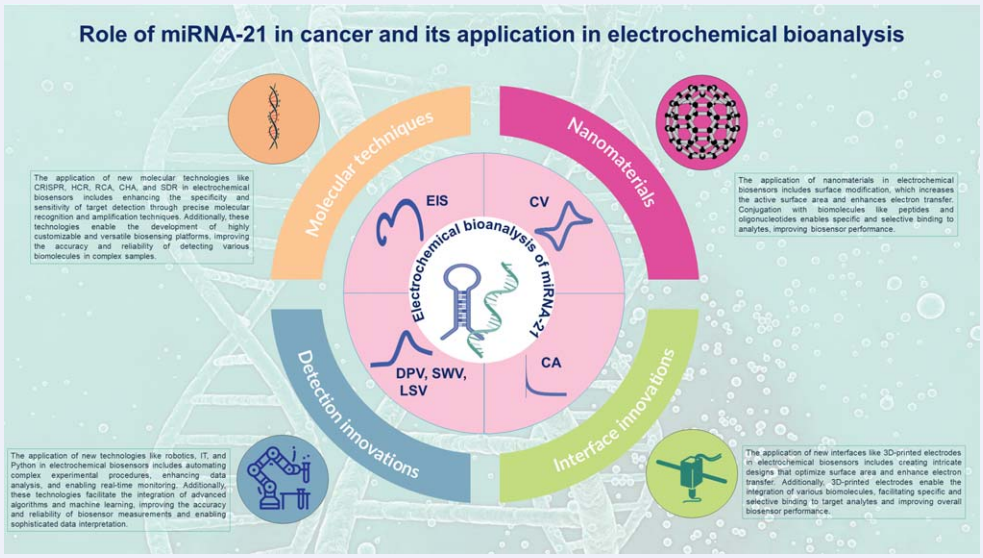
GRAPHICAL ABSTRACT



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One of the most challenging issues nowadays is cancer's spread, and it is the number one cause of death for individuals in the USA who are younger than 85 years old [1]. It is estimated that there will be two million new cases of cancer diagnosed in the United States in 2024, and 29% will be prostate among all male cancers, while 32% will be breast among all female ones [1].

Cancer is a multifaceted disease characterized by the dysregulation of various cellular processes, prominently including cell cycle control and genetic integrity maintenance. Cell cycle regulators orchestrate the orderly progression of cells through growth, division and differentiation phases, ensuring genomic stability and tissue homeostasis. Cells become cancerous for two main reasons: the inactivation of tumor suppressor genes, the activation of oncogenes and mutations that result in apoptosis escape [2]. The only way to prevent cancer is to reduce exposure to known risk factors, which can lower the probability of getting cancer. Unfortunately for all people, there are chances, while research has shown that age increases a person's likelihood of developing tumors [3]. Modifiable factors such as age and non-modifiable reasons such as the environment must be considered. Despite the cancer incidence being high, no matter what is done in prevention, pointing out why effective management of the disease has assumed a very crucial role in improving patient outcomes.

The most important step toward improving cancer survival rates and life qualities for those affected is early detection and proper treatment [4,5]. After screening on different levels according to social class based on gender, considering other factors such as age may help identify specific communities that need more intensive surveillance, if any at all [6]. Now, imaging techniques such as CT scans, x-rays, MRI, ultrasound and PET are considered the most vital clinical methods for cancer diagnosis currently [6]. Endoscopy is also suggested as a diagnostic method [7]. In other cases, biopsy, genetic mutation analysis test and blood test are also considered other methods to diagnose this disease. Despite their

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importance in diagnosis, these procedures usually come with some limitations; those carried out through imaging may fail to capture cancers still in their early stages, while invasive techniques like biopsies are risky and not always possible. For instance, although noninvasive, blood tests could be insensitive or nonspecific toward early cancer detection. Hence, the need for more sensitive, specific and cost-effective diagnostic tools like biosensors is highlighted [8].

One group of cancer markers that has been scrutinized lately is miRNAs, which refer to very small noncoding RNA sequences averaging about 22 nucleotides long [9,10]. The standard role that miRNAs take is that of gene regulation. However, in cancer cells, they exhibit an irregular expression level. Thus, a decrease in their expression leads to the activation of oncogenes, while an increase beyond typical causes inactivation of tumor suppressor genes [10]. Consequently, monitoring miRNA levels could be very pivotal in early cancer detection. MiRNAs can be accessed easily from biofluids, mostly blood, urine and saliva. Their presence is stable even under different conditions or in the presence of nucleases, making them one of the most reliable cancer markers; besides helping to diagnose, they can also be used for the prognosis of cancers. Among the miRNAs, miRNA-21 (5′-UAGCUUAUCAGACUGAUGUUGA-3′; genomic location: 17q23.1) has attracted more attention and has been more studied in cancer diagnosis than others [11,12]. An elevation in this type of miRNA has been seen in numerous cancers, such as breast cancer, lung cancer, prostate cancer and pancreatic cancer, among others [10–12]. The direct implication of miRNA-21 with the malignancy of cancer cells can be traced back to its oncogenic ability against the tumor suppressor genes [11]. MiRNA-21 is a crucial oncogene as it post-transcriptionally targets and downregulates levels of various tumor suppressor genes, including but not limited to PTEN, PDCD4 and RECK, to disrupt apoptosis, proliferation and metastasis gene regulatory networks [13]. This results in increased cell survival, rapid division and high motility within the body, thereby enhancing the progression of malignant disease. So, to sum up, we can say that microRNA-21 is one of the most essential genes in cancer development, and it may serve as a reference point for finding new methods of treatment or diagnosis in this field [14]. For this reason, it is vital to create highly sensitive, selective diagnostic techniques for detecting miRNA-21, such as electrochemical biosensors, as they would allow the disease to be caught at its early stages and save more lives.

In connection with these facts, we should consider electrochemical biosensors since they are very sensitive, give quick responses, can be made at a low price, and even be used as portable devices [12,15]. According to our literature review, during the past 5 years, not less than 1000 scientific articles have been published on electrochemical biosensors based on various methods for miRNA-21 determination where differential pulse voltammetry, electrochemiluminescence, square wave voltammetry, photoelectrochemical and electrochemical impedance spectroscopy were usually applied. Different detection principles have been described in the context of electrochemical biosensors for detecting miRNAs. Before considering this issue, it is necessary to recall the basic structure of biosensors, including a biorecognition element, a signal transducer and a signal detector [16]. In these electrochemical biosensors, the biorecognition element must be a bioprobe capable of capturing miRNAs; such probes comprise complementary DNA and RNA probes, locked nucleic acid probes or even peptide nucleic acid probes [12,17–19]. The formation of such complexes alters the conditions of contributing agents in the biosensor assembly and changes readable detection signals. The concentrations of analytes may be raised to increase (signal-on) or decrease (signal-off) the electrical signals produced. Recognition of a miRNA by its complementary probe leads to alteration in electrochemical signals, usually measured through impedance or current. It is a very sensitive and specific approach to detection.

It is important to increase the sensitivity, detection range and reliability of electrochemical biosensors [20]. Improving the signal transducer can achieve signal amplification, which is realized by focusing on modified surfaces. The interactive surface of signal interfaces can be modified with nanomaterials due to their specific enhanced physiochemical properties [21–23]. Furthermore, low-cost materials should be used during production, and lower-resistance materials should be employed as signal interfaces [24,25]. The best selections always involve unifying advanced materials such as nanomaterials and using a new generation of polymer-based materials for signal interface fabrication. There were other amplifications of signals made in electrochemical biosensors. These kinds of amplification agents always have direct or indirect interaction with probes. An important example is using conjugated nanomaterials with biomolecules, particularly macromolecules [12,26]. The other main option for signal amplification lies in molecular techniques, which allow better interaction between biorecognition elements and analyte molecules, as well as signal transducers [27]. Common among these molecular techniques are hybridization chain reaction, exonuclease-assisted target recycling, rolling circle amplification, catalytic hairpin assembly, strand displacement reaction and even CRISPR-Cas systems [28–30].

Electrochemical biosensors are used to detect miRNA-21, which assists in the early diagnosis of several cancers; however, other patient symptoms should also be considered since miRNAs are not specific cancer markers [31–33]. It would be advisable for future studies to focus more on multiplexing platforms that offer simultaneous detection of several cancer markers. Moreover, it is achievable to create novel signal interfaces coupled with applying optimized advanced materials to enhance overall sensing platform performance. Finally, electrochemistry can be integrated with other techniques like Raman spectroscopy and UV-Vis, among others, and even with IT and robotic technologies for improved miRNA-21 detection.

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