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Various types of electrochemical biosensors for leukemia detection and therapeutic approaches

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ABSTRACT

Leukemia often initiates following dysfunctions in hematopoietic stem cells lineages. Various types of leukemia, including acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), acute promyelocytic leukemia (APL), and human T-cell leukemia/lymphoma virus type 1 (HTLV-1) can thus call for different diagnosis and treatment options. One of the most important subjects in leukemia is the early detection of the disease for effective therapeutic purposes. In this respect, biosensors detecting the molecules of deoxyribonucleic acid (DNA) as analytes are called genosensors or DNA biosensors. Electrochemical sensors, as the most significant approach, also involve reacting of chemical solutions with sensors to generate electrical signals proportional to analyte concentrations. Biosensors can further help detect cancer cells in the early stages of the disease. Moreover, electrochemical biosensors, developed based on various nanomaterials (NMs), can increase sensitivity to the detection of leukemia-related genes, e.g., BCR/ABL as a fusion gene and promyelocytic leukemia/retinoic acid receptor alpha (PML/RARα). Therefore, the present review reflects on previous studies recruiting different NMs for leukemia detection.

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1. Introduction

Detection of cancer cells is an important issue because most of therapeutic methods for this condition are simply effective when diagnosed early. Leukemia initiates following dysfunctions in myeloid stem cells and lymphoid lineages and it is categorized using a combination of cytochemical, morphologic, cytogenetic, and immunophenotypic studies [1]. Acute leukemia is thus known as a heterogeneous member of malignant disorders of hematopoietic progenitor cells (HPCs) with various clinical characteristics, variable outcomes with currently available therapies, and molecular genetic abnormalities [2]. This type of leukemia usually occurs in children around the age of two or three years and manifests an abrupt onset [3]. On the other hand, chronic leukemia is mostly observed in older patients [3]. Conventional methods to detect leukemia commonly involve bone marrow examination, cytogenetic methods, and blood tests [4,5]. However, these traditional techniques have some disadvantages such as impractical testing equipment and procedural complications for clinical uses [6]. Biosensor technology can accordingly improve the quality of human life through its capacity in sensitive and selective monitoring as well as rapid detection of diseases [7]. In this review, a number of studies performed to detect different types of leukemia via electrochemical biosensors are examined.

2. Different types of leukemia

Previously leukemia could be categorized, based on the morphology of the blood cells, into the French-American-British (FAB) classification systems and then the World Health Organization (WHO) classification system, which were critical to understand the basics of this classification for the communication and understanding of disease states in patients [8]. Prognosis of leukemia is highly dependent on patient characteristics and its type at the time of diagnosis [9]. Therefore, the early diagnosis of this condition can help avoid missing recurrence and guide treatment discussions [10]. Leukemia cells are mostly originated from early blood-forming cells, which are often white blood cells. There are likewise several types of leukemia, mainly based on whether it begins in lymphoid or myeloid cells, and if it is acute (viz. fast-growing) or chronic (i.e., slow-growing) [11].

Various types of leukemia can call for different diagnosis and treatment options. In this sense, acute lymphocytic leukemia (ALL) starts in the bone marrow and it is more common in children than adults [12]. Acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) are prevalent in adults [13]. As well, chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML) are other types of the disease, which are initiated in blood-forming cells [14]. Children affected with ALL accordingly have some common presenting symptoms and signs, including lethargy, bleeding, fever, musculoskeletal symptoms, and lymphadenopathy [15,16]. AML accounts for 80% of acute types of leukemia in adults [17] with constitutional symptoms such as shortness of breath, fatigue, weight loss, and anemia [18]. Nearly 50% of adults with chronic leukemia suffer from CLL and 20% of them have CML [19]. Therefore, it is crucial to fulfill an early diagnosis of different leukemia cells through sensitive tools before signs appear in order to treat patients better.

3. Electrochemical biosensors

Electrochemical sensors, as the most significant approach, involve reacting of chemical solutions with sensors to generate electrical signals proportional to analyte concentrations [20]. The components of electrochemical sensors are reference electrode and sensing (that is, working) electrode separated by an electrolyte [21]. Such sensors have several advantages, making them attractive diagnostic devices in medicine, including inexpensive electrodes that can be easily integrated with simple electronics to perform fast measurements, monitoring of existing environmental conditions, and the ability to determine analyte concentrations within a complex sample at point-of-care (POC) testing, and simplicity.

Different electrochemical techniques such as potentiometric, impedimetric, and amperometric sensors can be thus practiced for biosensing applications [22]. In this respect, amperometric biosensors can transduce biological recognition events into current signals for the quantification of analytes by electroactive species [23]. In the most impedimetric biosensors, the Electrochemical Impedance Spectroscopy (EIS) can produce valuable data about physico-chemical changes once analytes bind to a bioreceptor immobilized on an electrode [24]. A potentiometric biosensor can also measure potential changes for the formation of interactions between bioreceptors and analytes [25,26]. Among several important advantages of potentiometric sensors are uses in miniaturization and automation of solid-state sensors [27].

4. Electrochemical biosensors and cancer cells

In recent years, different biorecognition elements including complementary nucleic acids, antibodies, aptamers, and other specific materials and molecules immobilized on a transducer surface, have been developed [28]. Biosensors used to detect cancer cells usually apply optical, electrochemical, and mass-based transducers [29]. Even though previous studies have thus far demonstrated numerous advantages of cancer biosensors, there are some challenges such as reduced sensitivity of detection due to weak biological signals produced via biomarkers and interaction of biorecognition molecules as well as decreased stability related to no biocompatibility of immobilization matrices [30].

One of the essential goals in developing sensitive electrochemical biosensors is the detection of cancer cells in the early stages of the disease. Therefore, some materials such as nanoparticles (NPs) and graphene quantum dots (GQDs) are being developed. NPs are widely exploited in cancer electrochemical sensors as they exhibit increased surface area, shape tunability, as well as electronic and size properties [31]. Nanomaterials (NMS) have various roles in biosensors with their thermal [32], extraordinary optical [33], catalytic [34], drug magnetic targeting [35], easy functionalization [36] and electronic properties [37]. Moreover, use of GQDs has been highly enhanced in cancer diagnosis [38]. Other NMs like nanowires, composite NMs, and nanocantilevers have been further immobilized on electrodes to detect cancer cells [39]. The strategy of using NMs in electrochemical biosensors, as an interfacial film between the transducer surface and biorecognition element, is thus to facilitate the processes of biosensor signals and electron transfers [40].

5. Nano-based electrochemical biosensors for leukemia detection

5.1. CML

5.1.1. Efficiency of drug and drug resistance

The multidrug resistance protein 1 (MDR1) gene encodes p-glycoprotein (P-gp), as a member transporter protein expressed on leukemia cells [41]. The P-gp accordingly has two membrane-spanning and two nucleotide-binding domains and it plays the role of an energy-dependent pump that decreases intracellular drug concentrations and finally causes chemotherapy failure [42]. Recognition of P-gp is thus of utmost importance for detecting of leukemia drug-resistance cells [43]. Studies have further reported some conventional methods such as enzyme-linked immunosorbent assay (ELISA), flow cytometry (FC), fluorescence (FL), and immunohistochemistry (IHC) as devices for P-gp detection [44,45]. These techniques generally need technical skills, time, and multiple steps. Polyaniline nanofibers (PANI-NFs) are attractive to be utilized in electrochemical biosensors because of their better biocompatibility and low cytotoxicity [46]. In this regard, Zhang et al. [44] detected P-gp on human ADM-resistant leukemia cell line (K562/ADM cells) through modified biosensors with gold (Au) and

PANI-NF NPs with a low detection limit and a wide linear range. Gulati et al. [47] also utilized single-walled carbon nanotubes (SWCNTs) for the detection of CML cells because of their attractive properties such as high surface area to volume ratio and diagnosed CML P-gp positive cells with the concentration of 1.5×10^5 cells per ml. Apoptosis refers to a process that has a crucial role in cellular metabolism, normal cellular homeostasis, and different diseases with characteristics such as decreased or increased cell survival [48]. In this respect, B-cell lymphoma-2 (Bcl-2) family is a crucial regulator, contributing to apoptosis progression or inhibition [49,50]. As well, Bcl-2 protein is one of the Bcl-2 family members, which can effectively suppress apoptosis via several potential pathways inhibiting oxidation, changing cell cycle rates, preventing calcium ions (Ca^{2+}) release, and interacting with Bcl-2-associated X (Bax) as the heterodimer (namely, Bcl-2-Bax) [51]. Bax can thus enhance apoptosis either through promoting the release of cytochrome C or generating homodimers (viz. Bax-Bax) [52]. Some therapeutic methods such as the use of imatinib, interferon-alpha (INF-α), gene therapeutics, and bone marrow transplantation can be accordingly effective in the apoptosis of CML cells [53]. Therefore, it is necessary to diagnose and assess CML apoptosis by detecting Bax and Bcl-2 proteins. FC, Western blotting, ELISA, and gel electrophoresis are the old technologies for Bax and Bcl-2 expression detection [54,55]. These methods need complex sample processing, precise instruments, and expensive costs. In this line, Zhou et al. [56] fabricated a new electrochemical biosensor to detect Bcl-2 and Bax after suppressing CML cells via imatinib. In this biosensor, reduced graphene oxide (RGO) as a substrate was firstly introduced on a GCE to elevate the surface area, modified with the antibodies I of Bcl-2 and Bax, and then the modified electrode was immersed into the mixed antigens to capture active Bax and Bcl-2. Mesoporous silica (Sio_2) amplification and CdSeTe@CdS quantum dots (QDs) and silver (Ag) nanoclusters were further employed as signal probes, which were proportional to the Bax and Bcl-2 antigens. Sio2 and nanoclusters can thus cause a large surface area. Bcl-2 and Bax proteins were also detected indirectly by using stripping voltammetry (ASV), and concentration range from 1 ng/ml to 250 ng/ml [56]. Moreover, Akhavan and his colleagues [57] have constructed a spongy graphene electrode (SGEs) via utilizing electrophoretic deposition (EPD) of chemically exfoliated GO materials on graphite surface and this modified electrode could detect one K562 cell in~ 10^9 normal cells in blood samples. This study led the same authors to investigate the effect of graphene sheets for extracting nucleic acids (NAs) from various cells and approved the ability of graphene materials in easy gene extraction [58]. And finally, this finding paved the way for the subsequent study to extract guanine from K562 CML cells using GO nanoplatelets (GONP) [59]. The differential pulse voltammetry (DPV) technique exhibited the different concentrations of guanine in the blood serum samples by GONP electrode with~ 10^{-11} LOD. The most important suggestion that can be made from these studies is that graphene sheets can employ in the diagnosis of other types of leukemia.

Poly(L-lysine) (PLL) has some advantages such as appropriate solubility in water, high active amino groups, excellent biocompatibility, and flexible molecular backbone and combining of materials like graphene and PLL, has additional properties [60]. So, in the study that have been done by Zhang et al. [61], combining of GO and PLL as a biocompatible film was immobilized on the electrode. Then, the K562 CML cells were detected by electrochemical impedance spectroscopy (EIS) technique with 30 cells ml^{-1} LOD.

5.1.2. BCR/ABL fusion gene

Active breakpoint cluster region (BCR)/abelson (ABL) oncoprotein could similarly induce CML cell pathogenesis [62]. As well, dasatinib is a multikinase inhibitor, which suppresses CML cells by inhibiting the activity of the adenosine triphosphate (ATP)-binding site of BCR/ABL to increase apoptosis and decrease proliferation of CML cells [63,64]. Moreover, caspase-3 (CASP-3) is a cysteine protease that is active in the early stage of apoptosis. Detecting the activity of CASP-3 can be thus an important object to evaluate the therapeutic effect of dasatinib [65]. Electrochemical sensors using glassy carbon electrode (GCE) modified with Au NPs/poly (diallyldimethylammonium chloride) (PDDA)/CNT and biotin-DEVD peptide can attach to nanolayers via thiol groups of the Au NPs and terminal cysteine residues. Then, the sensor is immersed into CASP-3 lysate and sensing CASP-3 is performed by DPV signals [66]. Molybdenum disulfide (MoS_2) is also a transition metal used in a number of electroanalytical, catalytic, and nanoelectronic fields for its unique magnetic and electrochemical properties as well as large specific areas [67,68]. Besides, PANI nanostructures (NSs) provide high adsorption ability and enhance active surface area [69]. To prevent some limitations of PANI such as insolubility, bad process ability, and poor mechanical strength, the composite of PANI and MoS_2 have been so far generated. The PANI-MoS_2 nanocomposite (NC) has strong coordination bond of nitrogen (N) atoms in PANI and metal Mo. Moreover, this NC produces highly electrocatalytic ability [70]. In the biosensor, the PANI-MoS_2 composite is employed in electrochemical deoxyribonucleic acid (DNA)-based types [71]. In this sense, Soni et al. [72] employed PANI nanospindles (NSs) to synthetize edge-rich integrated three-dimensional (3D) hybrid PANI-MoS_2 nano-flowers immobilized on electrodes to generate electrochemical genosensors for CML with a wide range of target DNA concentrations. Au NP/PANI hybrid composite can be further utilized in the electrochemical DNA biosensor for its properties, i.e., high selectivity and specificity, to detect BCR/ABL fusion gene in patients with leukemia via the interaction of DNA probe and DNA target. This sensor is considered as an attractive and simple device for the detection of the BCR/ABL oncogene in early-stage cases of leukemia [73].

Besides, aptamers as selected nucleic acid oligomers have high affinity or specificity against some small proteins, cells, and molecules [74]. Aptamer-based sensors have been accordingly developed for the diagnosis of cancers via electrochemistry, chemiluminescence, FL, and so on [75,76]. Chitosan (CS) is a natural cationic polysaccharide with some characteristics including biocompatibility, hydrophilicity, chemical stability, biodegradability and muco-adhesive properties, that can be effective in biomedical applications [77]. To solve this problem, QDs can be encapsulated via a polymer matrix, which has been proved to possess reactive functional groups for immobilization of biomolecules. As well, surface functionalization of QDs with CS may be appropriate for enhanced affinity towards DNA molecules, owing to the interactions between anionic phosphodiester backbone of DNA and cationic amino groups [78]. CS encapsulated cadmium telluride (CdTe)-QDs have further deposited onto indium tin oxide (ITO) glassy electrodes using electrophoretic deposition (EPD) technique and this biosensor can detect target BCR-ABL fusion gene from patients affected with CML as low as 2.56 pM concentrations (Fig. 1) [79]. Moreover, deposition of tri-n-octylphosphine oxide-capped cadmium selenide quantum dots (QCdSe) onto ITO glass substrate by the Langmuir-Blodgett (LB) technique can be connected with DNA probe, which can recognize CML-positive cell samples via Cd-thiol affinity [80]. Catalyzed hairpin assembly (CHA) is also known as a cost-effective amplification, developed from DNA NM organization [81]. CHA can thus achieve polynomial and exponential amplification and it has been widely employed for the analysis of nucleic acids, small molecules, and proteins [81]. CHA sequences are thus critical for various kinds of single-standard DNA inputs. Normal catalyst strand for CHA is accordingly categorized into three domains with 8 nt of each domain and target DNAs can be directly used as catalyst strand sequences for CHA, which need approximately 24 nt to limit the versatility of CHA [82]. Using NCs such as graphene sheet (GS), Au NPs, or PANI with CHA are accordingly excellent for improving signal amplification [83]. CHA and GS/PANI/Au NP sensing systems have provided high specificity and sensitivity for the detection of BCR/ABL [83]. As mentioned, nanostructured oxides of metals likes iron (Fe), zinc (Zn), and titanium (Ti) have been proved to have an important role because of their desired orientation to biomolecules with negligible conformational changes [84]. ZnO NPs have been expansively

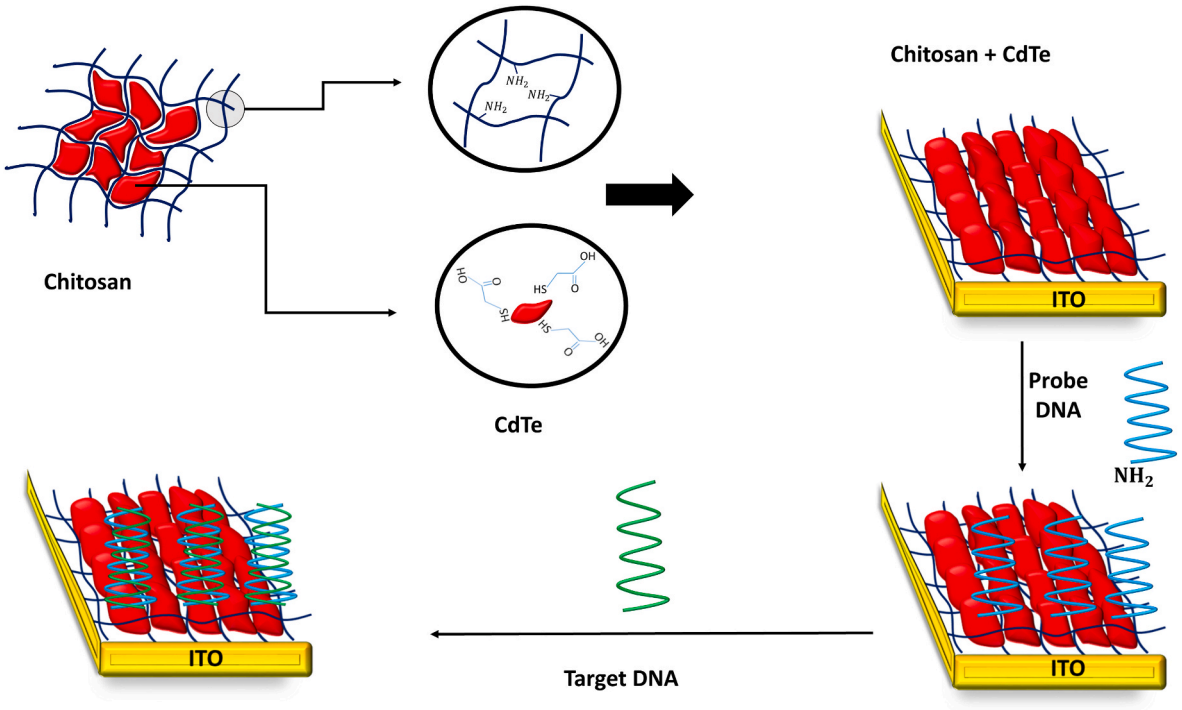

Fig. 1. Schematic representation of the BCR/Abl genes in CML patients. A electrochemical biosensor that modified by Chitosan, CdTe can detect BCR/Abl fusion gene with 2.56 LOD. Chitosan and CdTe bind with each other via _HS and _NH2 groups.

utilized in sensors due to their easy biocompatibility, fabrication, and non-toxic synthesis route[30]. As well, ZnO is a wide band gap semiconductor, which is more powerful for the modification of high-efficiency nano-devices [85]. In this sense, Pandey et al. [86] prepared an electrochemical sensor, modified with amino-functionalized silica-coated ZnO (Am–Si@Zno) onto an ITO-coated glass substrate and detected CML via covalently immobilizing the amino-terminated oligonucleotide probe sequence by glutaraldehyde as a cross linker [86]. In this study, EIS could diagnose CML with a detection limit of 1×10^{-16} M. The production and reduction of GO could depend on the use of explosive or toxic chemicals, including hydrazine, potassium permanganate ($KMnO_4$) and sulfuric acid or complicated and long processes [87]. The remaining chemical groups and the formation of defects in graphene can also induce the crystalline structure and electronic features of synthesized graphene, which are not well preserved [88]. The liquid-phase exfoliation (LPE) of graphite powder in the presence of ionic liquids and organic solvents (namely, exogenous materials) can thus exceed experimental steps, including the use of electrochemical potentials and sometimes sonication process, as a promising cost-effective method for scalable generation of conductive few-layer graphene (FLG) using available simple devices [89]. The LPE of graphite via the sonication of graphite powder in hemoglobin-capped Au NCs (Hb@AuNCs) is to obtain graphene nanosheets with high affinity for biomolecules[31]. Shamsipur et al. [90] Firstly modified electrodes with Hb@AuNCs and immobilized single-stranded (ss) DNA as the biorecognition elements of BCR/ABL gene of CML cells. Then, methylene blue was added as a signaling probe into the ssDNA and the voltammetric detection of the target complementary DNA (cDNA) over a dynamic linear range (DLR) of 0.1 fM to 10 pM [90].

5.1.3. Detection using the intrinsic property of the CML leukemic cells

Peroxidase mimetic materials compared with natural enzymes have been commonly used in many fields due to their excellent flexibility, satisfactory catalytic efficiency, high stability, and low preparation costs [91]. Hybrid peroxidase mimetic materials based on soluble GO can thus provide higher adsorption capacity and large specific surface [92]. Studies in this domain have reflected on the detection of cancer cells by sensors based on hemin modified graphene oxide (H-RGO) and Au nanorods with increased catalytic activity of three GO-family materials such as H-RGO-Au nanorods, H-RGO-Au NPs, and newly-presented H-RGO-Au nanoflowers prepared via enzyme kinetics experiments with 3,3′,5,5′-tetramethylbenzidine (TMB) and hydrogen peroxide (H_2O_2) as substrates. Liu et al. [93] Correspondingly modified new aptamer-based electrochemical sensors with mimetic peroxidase catalytic activity of H-RGO-Au NFs and diagnosis of K562 cancerous cells. It should be noted that reactive oxygen species (ROS), containing peroxynitrite ($ONOO^-$), hydroxyl radical (OH), H_2O_2, superoxide onion (O_2^-), and so on, can thus result in oxidative damage to lipids, nucleic acids, and proteins, due to cell death and mutagenesis [94]. High activity of O_2^- also occurs in hypoxia, ischemia-reperfusion, and traumatic brain injury, which adds to the body's natural ability to deal with the potentially cytotoxic species and contribute to the etiology of progressive neurodegenerative diseases, cancer, and aging [95,96]. O_2^- is generated at a rate that is matched via the capacity of tissues to catabolize them, so holding a rather low concentration under normal physiological conditions [94]. As well, potassium (K) is one of the elements for chemical doping, as a potential strategy to increase thermal or electrical conductivities for the chemical doping carbon NTs [97]. K-doped multi-walled carbon NTs (KMWNTs) can thus elevate the sensitivity and biocompatibility of carbon NTs in biosensing applications [98]. To modify physical and chemical properties of KMWNTs, researchers have made use of ammonium ion (NH_4^+)-based molten salts because of their high electrochemical conductivity, very low vapor pressure, and high stability [99]. Using the 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM) and the interaction of cation-π with KMWNTs can also produce synergic effects to accelerate electron transfer between electrode and redox probe [100]. The KMWNT-BMIM modified electrodes can detect superoxide anions, released from leukemia cancer cells with 0.024 μM detection limits [100]. For example, Yi et al. [101] Demonstrated that high surface activity of QDs accompanied by low interaction with biological molecules could be due to agglomeration of QDs and bioconjugates.

5.2. APL

APL is a clonal expansion of hematopoietic precursors, which happens by a 15:17 chromosome translocation, with breakpoints within promyelocytic leukemia on chromosome 15 and the retinoic acid receptor alpha (RARα) gene on chromosome 17[12]. Thus, the PML/RARα fusion gene is a critical biomarker of APL type of cancer, and it is present in approximately 100% of cases [102]. Nanoporous gold (NPG) is highly applied thanks to its properties, including biocompatibility, superior conductivity, large surface area, and high stability [103]. It is synthesized by several methods such as organic templating [104], electrochemical deposition [105], liquid-crystal templating (LCT) [106], and repetitive square-wave oxidation-reduction cycle (SWORC) [107].

The early detection of this disease is necessary because of the correlated life-threatening coagulopathy and the unique response of the disorders to all-trans retinoic acid (ATRA) therapy. The biosensor based on NPG-modified electrode can evaluate the PML/RARα fusion gene via DPV with a concentration range of 60pM–220pM [108]. CNTs, due to their desirable and unique physicochemical advantages, including strength electrocatalytic and conductivity activity and large surface areas, have been extensively applied in electrochemical fields [109]. Combining FePt NPs and CNTs can thus elevate the electron-transfer process on the electrode and lead to better sensing behavior for the PML/RARα fusion gene with a 2.1×10^{-13} mol/L detection limit [110]. In many NA biosensors, the interaction between DNA probes and complementary sequence assays can thus have significant effects on the performance of DNA sensors primarily via the selection of probes and hybridization conditions [111]. Short DNA electrochemical probes also have some disadvantages, such as poor specificity, sensitivity, and stability. So, novel oligonucleotide derivatives as a locked nucleic acid (LNA) were described in 1998 [112]. LNA nucleotides have a methylene bridge between the 4′-carbon and 2′-oxygen of the ribose moiety. The given bridge can effectively increase the local organization of the phosphate backbone, lock the furanose ring in the C′3-endo conformation, and reduce the conformational flexibility of the ribose [113]. As well, peculiar features, including enhanced triplex formation, low toxicity, availability from a commercial supplier, and synthesis by standard methods are among other benefits of LNAs [114]. High background signals can also be generated via lower sensitivity, restricted diagnosis specificity, range of typical intercalator-based DNA sensors, and non-specific binding of intercalators to non-hybridized ssDNA [115]. To solve the mentioned problems, sandwich electrochemical DNA sensing and electrochemistry combined with enzyme-labelled bioelectrical catalytic reaction was fabricated by Zhang et al. [116]. As well, Wang et al. [117] firstly immobilized capture LNA probe on Au electrode through Au–S bonding. In this study, the biotinylated reporter probe and the capture probe franked the target sequence to form the sandwich-sensing mode. Such probes can be thus connected with streptavidin-horseradish peroxidase (streptavidin-HRP) and this electrochemical sensor offers an enzymatically amplified electrochemical current signal for the diagnosis of PML/RARα fusion gene in APL patients with a detection limit of 74 fM (Fig. 2) [117]. The location of the ssDNA probe at a transducer surface is accordingly important due to high accessibility, biological activity, excellent orientation propitious to duplex formation with the DNA target, and a short distance between the electrode surface and duplex [118]. In traditional methods, polymers such as polyaniline and polypyrrole have been similarly used for DNA probe immobilization [119]. However, the main drawbacks of these polymers are relatively high and complicated synthesis and toxicity that critically restrict their operation in bioelectrochemistry. Moreover, xanthurenic acid (Xa) is a product of the tryptophan-NAD process, correlated with different pathological conditions since it has low toxicity [120]. Iron oxide (Fe_2O_3) as an environmental-friendly n-type semiconductor oxide has been applied as a substrate because of some properties, including easy preparation process, low toxicity, and high conductivity [121]. Xa also operates as a potent iron chelator and the hydroxyl group in the 8-position of the quinoline moiety is crucial for the binding of Fe [122]. The PML/RARα fusion gene probe has been covalently attached to the carboxyl-terminated pXa/Fe_2O_3 nanomembranes via the free amines of DNA sequences based on the N-hydrosulfosuccinimide and 1-ethyl-3- (3-dimethylamino propyl) cross-linking reaction [123]. The EIS, modified with pXa/Fe_2O_3 nanorhombus membranes, can thus detect the PML/RARα fusion genes [123] (Table 1).

5.3. Other types of acute leukemia and HTLV-1

Acute leukemia remains one of the main cancer causes of mortality in developed countries. Carcinoembryonic antigen (CEA or CD66) is one of the cancer biomarker family members, whose expression has been proved in blasts from children affected with ALL [124]. Previously, PCR and ELISA kite were two Au standard tests for CEA diagnosis. Mazloum et al. [125] also prepared a CEA aptamer-based biosensor modified with Au NPs on GCE and utilized four electrochemical methods such as EIS, chronoamperometry, DPV, and cyclic voltammetry (CV). In this work, the concentration of the target antigen ranged from 10 pM to 100 μM. Poly (catechol) is an appropriate polymer with redox behavior but disadvantages when it synthesizes with the aid of enzymes such as multiple

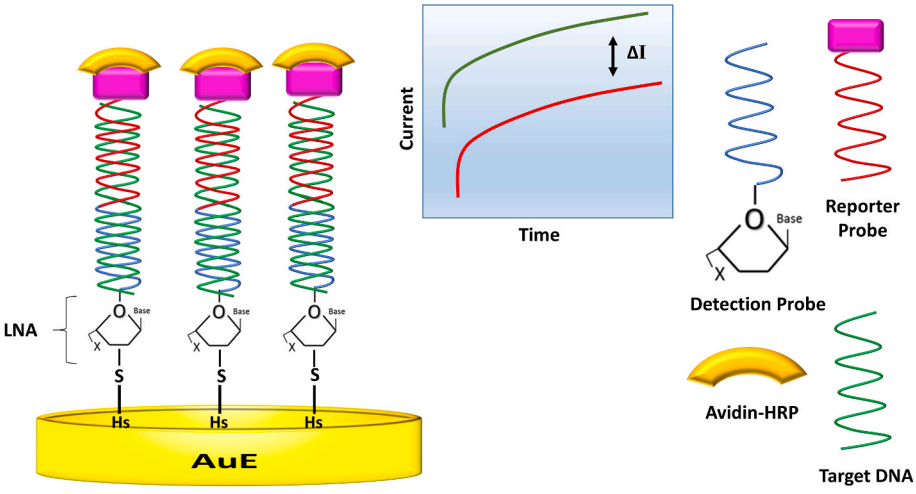

Fig. 2. Schematic representation of the Sandwich method of PML/RARα fusion gene detection in APL patients. Firstly LNA binds with HS group on Au electrode and biotinyl reporter probe as an affinity tag for streptavidin–horseradish peroxidase (streptavidin–HRP).

Table 1
Different type of electrochemical biosensors for detection of leukemia.

Sensing Platform	Transduction Type	disease	Target	LOD	Reference
Au/PANI-NF	**CV, EIS**	**K562/ADM Leukemia**	**P-gp**	**80 cell/ml**	[44]
SWCNTs	**CV, EIS**	**CML**	**P-gp**	**19 cells/ml**	[47]
AuNPs/PDDA/CNT	**DPV**	**CML**	**Caspase-3**	**-**	[66]
PANI-MoS2	**EIS**	**CML**	**BCR/ABL**	**3x10^{-18} M**	[72]
RGO/SiO2	**ASV**	**CML**	**BCL-2, Bax**	**1 × 103 cells**	[56]
RGO	**DPV**	**CML**	**K562 cells**	one cell in 10^{9} normal cells	[57]
GO nanoplatelets	**DPV**	**CML**	**K562 cells**	10^{-11} cells	[59]
CuS-GR	**EIS, CV**	**Acute Leukemia**	**CCRF-CEM**	18 cell ml^{-1}	[128]
KMWNT-BMIM	**CV**	**Human Leukemia cell lines**	**SOD**	**0.024 μM**	[100]
CdTe-QDs	**CV, DPV**	**CML**	**BCR/ABL**	**2.56 pM**	[137]
QCdSe	**CV**	**CML**	**BCR/ABL**	**10 fM**	[80]
CHA/GS/PANI/AuNPs	**DPV,EIS**	**CML**	**BCR/ABL**	**1.05pM**	[79]
Am–Si@Zno	**EIS**	**CML**	**BCR/ABL**	**1x10–16 M**	[86]
Hb@AuNCs	**EIS, CV**	**CML**	**BCR/ABL**	**0.037 fM**	[90]
NPG	**DPV**	**APL**	**PML/RARα**	**6.7pM**	[108]
FePt/CNTs	**EIS**	**APL**	**PML/RARα**	**2.1 x 10–13 mol/L**	[110]
LNA/Au	**CV, EIS**	**APL**	**PML/RARα**	**74 fM**	[117]
pXa/Fe2O3	**CV**	**APL**	**PML/RARα**	**2.8 fmol/L**	[123]
Gold Nps/GCE	**DPV, EIS, CV**	**ALL**	**CEA**	**1.0pM**	[125]
rGo-PPY-(L-cys) AuNPs	**DPV**	**HTLV-1**	**HTLV-1 Tax gene**	**20 attomolar**	[136]

PANI: Polyaniline nanofibers, CV: Cyclic Voltametry, EIS: Electrochemical Impedence Spectroscopy, DPV: Differential Puls Voltametry, ASV: stripping voltammetry, PANI: poly-aniline, P-gp: p-glycoprotein, SWCNT: Single-wall Carbon nanotubes, CML: Chronic Myeloid Leukemia, BCR: Breakpoint Cluster Region, RGO: Reduced Graphene Oxide, Bax: Bcl-2-associated X, MoS2: Molybdenum disulfide, KMWNT: K-doped multi-walled carbon nanotubes, BMIM: 1-butyl-3-methylimidazolium hexafluorophosphate, QDs: Quantum Dots, CHA: Catalyzed Hairpin Assembly, GS: graphene sheet, Hb@AuNCs: hemoglobin-capped gold nanocluster, NPG: Nanoporous Gold, APL: Acute promyelocytic Leukemia, HTLV-1: Human T cell leukemia virus type 1, PPY: polypyrrole, copper sulfide and graphene (CuS-GR).

steps and high costs of enzymes, which can denature overtime [126]. Therefore, studies have shown that poly (catechol) without enzymes have merely developed for the modification of biosensors. One of the most important challenges of ALL disorders is that leukemia cells can spread to other organs without traveling in the blood. Therefore, the early detection of ALL with sensitive and selective biosensors is necessary [127]. The DNA electrochemical sensor was further modified and immobilized with poly (catechol) without expensive enzymes using graphene sheets and Au NPs for enhancing the conductivity of poly (catechol) [124]. In this work, the DNA concentration of ALL was prepared with a detection limit of 10 pM by four various robust methods, that is, CV, DPV, EIS, and chronoamperometry [124].

As mentioned in the 5.1.1 section, the combination of graphene with other nanoparticles can have more properties than each of them alone. For example, Sulfide nanomaterials have been highly utilized in different electrochemical biosensors [128]. A study by Khoshroo et al. [129] showed that the combination of copper sulfide and graphene (CuS-GR) could be an excellent electrode modifier for electrochemical detection of acute leukemia cells with 18 cell ml^{-1} LOD. This study demonstrates the importance of combining graphene with various nanomaterials to increase the sensitivity of the electrochemical biosensors.

One of the main diseases in several endemic regions such as Africa, Southern Japan, some parts of South America, and the Caribbean Basin is HTLV-1 [130]. HTLV-1 is correlated with two serious disorders containing HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ALT). Approximately, over 15–20 million people worldwide have HTLV-1 [131]. Pyrrole (Py) accordingly combines with rGO structure carbons due to the formation of the polypyrrole (PPy) layers [132]. PPys have been widely used in several studies to develop sensors because of their rapid electrochemical response and wide dynamic range [133]. Previous studies have also revealed that the pulsed amperometric detection (PAD) signals have increased by 6–7 times when target DNAs with platinum electrodes have been modified via ssDNA entrapped within polypyrrole (ssDNA/PPy) in comparison with blank PPy-deposited electrodes incubated in the target DNA solution [134]. Furthermore, the molecularly imprinted polypyrrole (MIPPY) layer immobilized on the carbon electrode surface is sensitive for target DNA [135]. In this sense, Fani et al. [136] fabricated a new electrochemical biosensor modified with rGo-PPY-(L-cys) Au NPs on screen-printed carbon electrode (SPCE) and detected HTLV-1 Tax gene using DPV (Table 1).

6. Conclusion

NPs are highly utilized in electrochemical genosensors for cancer detection as they exhibit enhanced surface area, shape tenability, as well as electronic and size properties. PANI-NFs, Hb@AuNCs, ZnO NPs, and H-RGO-Au nanoflowers are accordingly a number of NPs applied in electrochemical biosensors to detect BCR/ABL fusion gene in CML. For the diagnosis of PML/RARα gene in APL samples, recent studies have modified different electrochemical genosensors based on NMs including NPG and CNTs and have even used Au NPa and rGo-PPY-(L-cys) Au NPs for the sensing of target DNA in ALL and HTLV-1. Moreover, DPV, EIS, CV, and chronoamperometry are among electrochemical techniques utilized in these sensors with appropriate detection limits. Different devices containing of fluorescence in situ hybridization (FISH), real-time quantitative polymerase chain reaction (PCR), flow cytometry (FC), and traditional microscopy for morphology (TMM) are developed for evaluation of rearranged or mutant sequences and high-regulated leukemia related genes. Of note, these conventional methods for leukemia diagnosis have some disadvantages such as impractical testing equipment and procedural complications, so it is necessary to pay more attention to developing biosensing methods for other leukemia such as AML and CLL via new materials to elevate the specificity and sensitivity of these sensors in future studies. According to the contents of this review article, it can be concluded that the use of different nanomaterials for the design of electrochemical genosensors can have a significant impact on sensitivity. As mentioned, biosensors or genosensors are very cost-effective compared to other mentioned methods such as FISH and PCR. If future studies can further increase the sensitivity of nanomaterials-based electrodes, we will see the superiority of biosensors over other methods of leukemia detection. In addition, one of the critical perspective for the detection of leukemia by electrochemical biosensors is the combination of different nanomaterials to enhance sensitivity.

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The authors declare that they have no competing interests.

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