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REVIEW ARTICLE

Advances in the design of nanomaterial-based electrochemical affinity and enzymatic biosensors for metabolic biomarkers: A review

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Abstract

This review (with 340 refs) focuses on methods for specific and sensitive detection of metabolites for diagnostic purposes, with particular emphasis on electrochemical nanomaterial-based sensors. It also covers novel candidate metabolites as potential biomarkers for diseases such as neurodegenerative diseases, autism spectrum disorder and hepatitis. Following an introduction into the field of metabolic biomarkers, a first major section classifies electrochemical biosensors according to the bioreceptor type (enzymatic, immuno, apta and peptide based sensors). A next section covers applications of nanomaterials in electrochemical biosensing (with subsections on the classification of nanomaterials, electrochemical approaches for signal generation and amplification using nanomaterials, and on nanomaterials as tags). A next large sections treats candidate metabolic biomarkers for diagnosis of diseases (in the context with metabolomics), with subsections on biomarkers for neurodegenerative diseases, autism spectrum disorder and hepatitis. The Conclusion addresses current challenges and future perspectives.

Keywords Autism · Biosensing assays · Hepatitis · Neurodegenerative diseases

Introduction

The term "biomarker" was first used in 1989 as a measurable indicator of some biological states or conditions [1]. These traceable substances can be utilized for physiology-related assessments such as disease risk, psychiatric disorders, environmental exposure, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, etc. Biomarkers reflect the entire spectrum of diseases from the earliest manifestations to the terminal stages and are one of the driving forces of pharmaceutical research and drug development. They have been approved by the U.S. Food and Drug Administration (FDA) regulation for use as surrogate endpoints in the treatment development process [2]. Biomarkers are often cheaper and easier to measure than true endpoints. Furthermore, they can also be measured more quickly and earlier. Considering these advantages, biomarkers have tremendous potential to affect the success rate of clinical trials, identify new drug targets and develop diagnostic assays for early detection of diseases [3, 4].

The metabolic biomarkers known as an important class of biomarkers indicate changes in metabolic processes [5]. The role of metabolism in diseases is emerging as an area of etiopathological interest. Defining the differential alterations in metabolic pathways for a variety of disorders has become an increasingly accessible option for investigators and clinicians. The exponential growth of metabolomic analyses and their relevant scientific literature within the clinical biochemistry over the last decade provides evidence of the utility of such approaches in distinguishing between health and disease and in defining potentially targetable disease mechanisms. The deregulated levels of metabolites are observed in abnormalities or disorders such as neurodegenerative diseases [6, 7] and autism spectrum disorder (ASD) [8, 9]. In addition, altered metabolite levels can represent chronic infectious diseases such as hepatitis [10]. Therefore, a fast and reliable detection of these biomarkers can help medical professionals to differentiate between diseases showing similar symptoms.

Nowadays there is a growing interest in the development of devices for the specific and sensitive quantification of biomarkers. Electrochemical biosensors can play a key role in the development of low cost, portable and rapid sensing techniques for this purpose. They provide reliable

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electrical signals resulting from specific immunoreactions. During the last years, different biosensing platforms have been described for the detection of biomarkers. The high interest raised by this issue has been highlighted in the recent reviews devoted to the use of functionalized nanomaterials with biological receptors for low-level detection of metabolic biomarkers. The signal enhancement associated with the use of nanomaterials is an effective path for ultrasensitive biosensing of biomarkers [11].

With remarkable achievements in nanotechnology, the nanomaterials have attracted significant attention in the electrochemical biosensors not only for electrical signal amplification, but also for immobilizing biological probes on the electrode surface [12]. The inherent advantages of electrochemical biosensors are associated with unique chemical and physical properties of nanomaterials, such as outstanding electronic and catalytic characteristics, high surface to volume ratio and simple modification of their surfaces. They have active surfaces that can easily be modified for immobilization of numerous biomolecules [13]. In addition, the large specific surface area and high surface free energy of nanomaterials will lead to the preparation of a variety of surface-immobilized biomolecules with improved stability. It is important to note that direct adsorption onto bulk materials may result in biomolecule denaturation and loss of bioactivity, while nanosized materials not only show a strong tendency to adsorb biomolecules but also retain their bioactivity [14]. These features combined with the functioning of biomolecules contribute to the improvement of biosensor performance in terms of sensitivity and specificity.

This review provides an updated overview of selected examples during the period 2005–2018 involving electrochemical biosensing approaches and nanomaterial-assisted signal enhancement strategies, which have been applied for the determination of a wide range of metabolic biomarkers. The aim of this effort is to provide the reader with a concise view of advances in the field of electrochemical nanobiosensors for determination of metabolic biomarkers.

Classification of electrochemical bioassays according to the bioreceptor type

Compared to non-bioreceptor sensors, the receptor-based biosensors are of particular interest, due to the high specific and strong interaction of biological probes with their target molecules, which results in a more efficient and reversible attachment of the analyte and/or ligand.

The sensitivity and selectivity of these methods essentially depend on the properties of the biorecognition elements to be used for analyte binding [15]. Electrochemical biosensors, an important subclass of biosensors, combine the high specificity of the bioreceptor with the high sensitivity of electrochemical transducers. In general, the biosensors can be classified into five major classes, according to the bioreceptors used. The enzymes, antibodies and aptamers are the main classes of bioreceptors that are mostly used in biosensing applications (Fig. 1). Although antibodies and oligonucleotides have been widely employed, enzymes are by far the most commonly used biosensing elements in biosensors.

Electrochemical enzyme-based biosensors

The field of biosensors has grown enormously since the first demonstration of the glucose enzyme electrode concept by Clark and Lyons in 1962 [16]. The entire field of biosensors can trace its origin to this original enzyme electrode. From 1962 until now, considerable efforts have been made on the creation and evolution of new enzymatic biosensors as an exciting area of biochemical research, reflecting a growing emphasis on this technology.

Depending on the assay type, two fundamental classes of enzymatic biosensors can be distinguished. In the first group, the enzyme detects the presence of a substrate, or co-substrate/co-factor. A typical example is a glucose biosensor. The second group is based on the detection of inhibitors in the presence of a substrate. The most common example of this approach is the detection of organophosphate compounds used as pesticides or warfare nerve agents. The major advantage of these approaches is the high sensitivity and specificity of catalytically active enzymes towards their target molecules.

Notwithstanding all these advantages, the enzymes have some drawbacks that have limited their widespread application. They often suffer from lack of chemical and thermal stabilities. Exposure to certain conditions, such as elevated temperatures or organic solvents, can lead to denaturation and concomitant loss of activity. There have been significant improvements in the field of enzymatic biosensors. For example, the use of new genetically engineered enzymes has allowed the improved performance characteristics of current biosensors for the detection of established analytes. In fact, the application of modern engineering techniques in enzyme biosensors has enabled the optimization of their properties [17, 18].

Electrochemical antibody-based biosensors

Antibody-based biosensors known as immunosensors have revolutionized diagnostics for the detection of a variety of biomarkers [19, 20]. The first immunosensor reported in the 1950s opened the doors to the possibility of immunodiagnosis [21]. Since then, a widespread effort has been conducted to develop immunosensors for clinical diagnostics.

Antibodies, as a member of the biorecognition elements are categorized into two main classes of monoclonal and

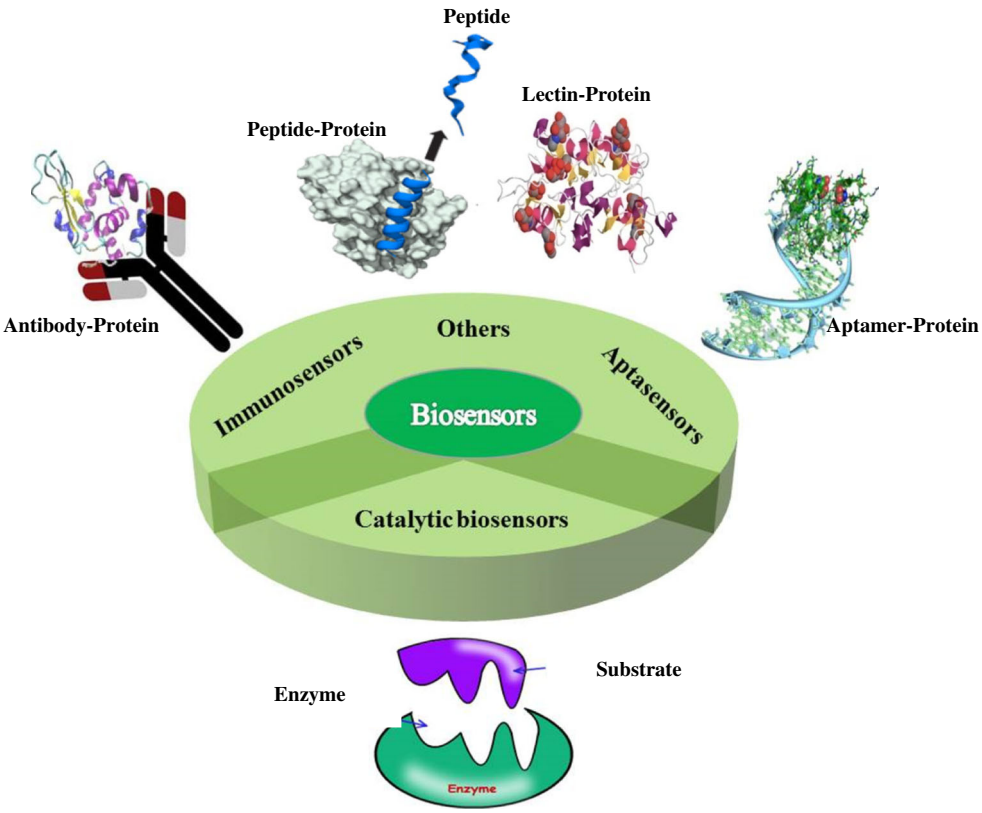

Fig. 1 The main classes of bioreceptors used in the biosensing applications

polyclonal antibodies. Monoclonal antibodies have a monovalent affinity, in that they specifically bind to the same epitope. In contrast, polyclonal antibodies bind to multiple epitopes and are usually made by several different plasma cell lineages. They have higher overall antibody affinity against the antigen due to the recognition of multiple epitopes of an antigen. Polyclonal antibodies can be produced in large quantities in a short time, without complicated technologies and at low cost; however, they suffer from lack of specificity [22]. Thus, for such applications as biosensing and therapeutic drug development that require antibodies specific to a single epitope, the monoclonal antibodies might be more apptopriate. They offer a combination of high specificity with an excellent ability for affinity purification. However, they have long production time and high cost.

Nanobodies (Nbs) as the single-domain antibody fragments derived from heavy-chain antibodies of camelids and cartilaginous fish were discovered in camelidae in the early 1990s [23]. Like a whole antibody, they are able to bind selectively to a specific antigen. In contrast to common antibodies, they are well expressed in microorganisms and are less lipophilic and more soluble in water [24]. Due to their low molecular weight, high physico-chemical stability and ability to bind antigens inaccessible to conventional antibodies, they have broadly used in biosensing applications. Theses single-domain antibodies can be coupled more densely on biosensor surfaces. In addition to their advantage in targeting less accessible epitopes, their conformational stability also leads to higher resistance to surface regeneration conditions.

Electrochemical aptamer-based biosensors

Aptamers are artificial single-stranded nucleic acid ligands that can bind a wide range of target molecules including small molecules [25], tumor markers [11], ions [26], proteins [27], cells [28] and tissues and organisms [29] with high specificity and selectivity. Aptamers are screened through an in vitro process called SELEX and can replace antibodies in different applications. Aptamers are similar to antibodies regarding their binding affinities, but they offer a number of advantages over antibodies such as chemical and thermal stability, adaptability to various targets, ease in synthesis and storage, and versatility in labeling, immobilization, signaling and regeneration [30]. These outstanding properties make the aptamers promising diagnostic and therapeutic tools for the future biomedical and analytical applications.

Since their discovery in 1990 [31–33], aptamers have demonstrated important advantages in the field of biosensing, especially for the development of devices that allow the detection of disease biomarkers. The first aptasensor proposed in 1998 for the detection of thrombin was based on the use of an aptamer labeled with a fluorescent marker [34]. Since then, a considerable advancement has occurred in biosensor design as well as the use of signal amplification probes to achieve small

molecules sensing. Although the potential biosensing applications are unlimited, most of the current applications are foreseen in the areas of biomarker detection, cancer clinical testing, and detection of infectious microorganisms and viruses [35].

Strategic applications of nanomaterials in electrochemical biosensing

The need for ultrasensitive bioassays and the trend towards miniaturized assays make the nanomaterials one of the hot fields in biosensor technology. Ever since the pioneering study of Mirkin and co-workers [36] on nanoparticle-based biosensors, a variety of nanostructured materials have demonstrated their appropriateness for biosensing applications. The intelligent use of nanomaterials can lead to clearly enhanced performances with increased sensitivities and lowered detection limits of several orders of magnitudes.

In this review, we will briefly describe the classification of nanomaterials and provide a brief overview of their role in the development of ultrasensitive electrochemical biosensors. Special attention is paid to the major role of nanomaterials as the signal amplifiers. Applications of nanoparticles in electrochemical signal amplification are mainly based on three mechanistic types: (1) nanomaterials that increase the loading of bioreceptors; (2) nanomaterials that act as the electrochemical signal generating probes; (3) nanomaterials that enhance the loading of electrochemically detectable species (Fig. 2).

Classification of nanomaterials

Nanomaterials are defined as materials in which at least one length dimension is below 100 nanometers. In this size regime, these materials exhibit particular and tunable optical, electrical and mechanical properties that are not present at the macro-scale. The synthesis of novel nanomaterials is a growing research area due to the potential applications for the progress of novel technologies. In the past two decades, hundreds of novel nanomaterials have been introduced. So, the preparation, characterization and classification of nanomaterials, as well as their applications, are essential.

The first classification idea of nanomaterials was given in 1995 [37] and further explained in 2000 [38]. A new classification scheme was reported in 2007 to overcome the limitations of previous classification methods [39]. In this scheme, the various types of nanostructures were discriminated based on their dimensionality. They were characterized as i) zero-dimensional (0D), ii) one-dimensional (1D), iii) two-dimensional (2D) and iv) three-dimensional (3D).

Zero-dimensional nanomaterials

Zero-dimensional nanomaterials are the elementary building blocks in the design of nanostructures, represented by nanoparticles, quantum dots and nanoclusters (Fig. 3a–c). All three dimensions of zero-dimensional nanomaterials are within 100 nm, more specifically less than 50 nm in the most cases.

One-dimensional nanomaterials

Nanostructures like nanotubes, nanorods, nanowires, nanobelts, nanoribbons and nanofibers with two dimensions in the nanoscale regime and the third dimension in the microscale are known as one-dimensional nanomaterials (Fig. 3d–i).

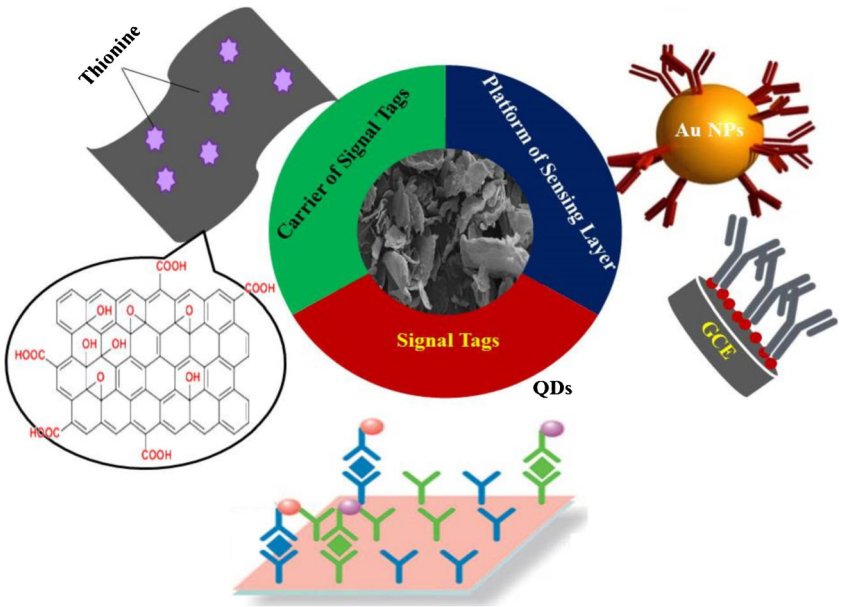

Fig. 2 Applications of nanomaterials in the electrochemical biosensing

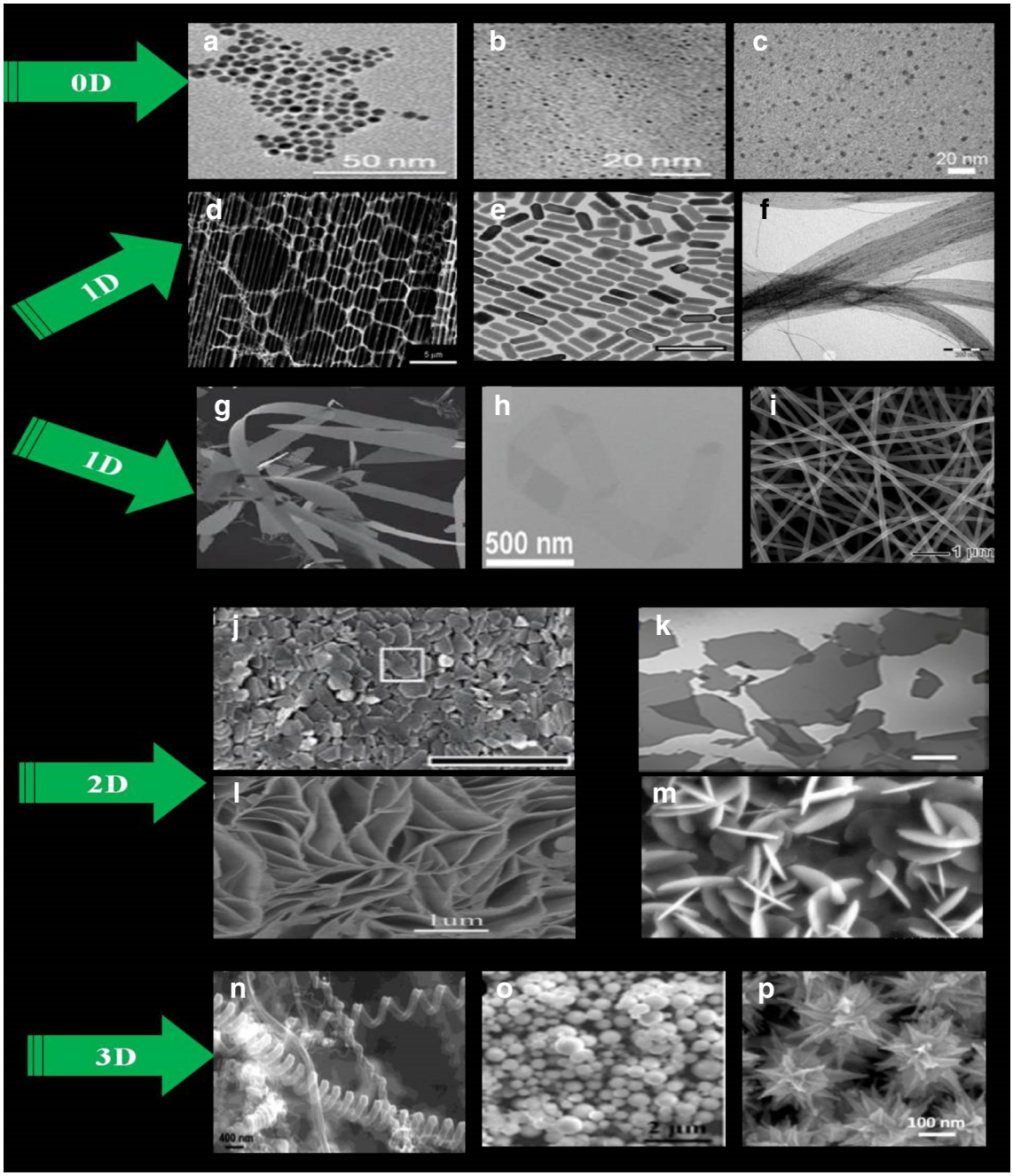

Fig. 3 Typical SEM and TEM images of different kinds of nanostructures based on their dimensionality; **a** Aunanoparticles [40], **b** Au nanoclusters [40], **c** carbon dots [41], **d** carbon nanotubes [42], **e** Au nanorods [43], **f** Au nanowires [44], **g** CdSe nanobelts [45], **h** graphene oxide nanoribbons [46], **i** ceramic nanofibers made of anatase and rutile [47], **j** Ag nanoplates [48], **k** graphene oxide nanosheets [49], **l** copper nanowalls [50], **m** silica nanodisks [51], **n** carbon nanocoils [52], **o** graphene nanoballs with copper cores [53], and **p** Pd nanoflowers [54]; Reprinted by permission of ACS Publishers

Two-dimensional nanomaterials

Two-dimensional nanomaterials are the thinnest materials with only one dimension whithin 100 nm whereas the other two dimensions are those of bulk materials. The common representations of two-dimensional nanomaterials are nanoplates, nanosheets nanowalls and nanodisks (Fig. 3j–m). These nanomaterials generally possess very high specific area and good aspect ratio.

Three-dimensional nanomaterials

Three-dimensional nanomaterials such as nanocoils, nanoballs and nanoflowers are nanophase materials consisting of equiaxed nanometer-sized grains (Fig. 3n–p). These nanomaterials have attracted intensive research interests because they have higher surface areas and supply enough absorption sites for all involved molecules in a small space.

Electrochemical signal amplification approaches using nanomaterials

The electrochemical signal amplification based on nanomaterials for obtaining lower and lower detection limit has recently attracted considerable attention due to the need for ultrasensitive bioassays. Especially, most nanomaterials are biocompatible, which permit them to act in direct contact with the biological environment. In order to achieve a good performance for biosensing, three approaches including biosensing nanoplatforms, signal generating nanoprobes and nanocarriers for signal probes in label-free sandwich detection strategies have been introduced.

Nanomaterials as the platforms of sensing elements

Nanotechnology offers unique opportunities for creating highly sensitive biosensing platforms. Electrode nanostructuration with nanoscale materials is currently a regular operation for preparing electrochemical scaffolds with improved conductivity and enhanced ability for immobilization of biomolecules. In fact, the stabilization of functionalized nanomaterials on the electrode surface increases the effective surface area and promotes the accumulation of bioreceptors. They act as signal amplification platforms for bioreceptors, owing to the existence of reactive groups on their surface, the fast electron transfer kinetics (particularly beneficial for electrochemical biosensors) and the high surface to volume ratio. It is widely believed that the large surface area to volume ratio is directly related to the high sensitivity of nanomaterials based biosensors. In addition, the ion centers and high electrical conductivity of some nanostructures can also have a major role in accelerating the electron transfer process.

A wide variety of electroconductive or semi-electroconductive nanomaterials with small sizes and appropriate surface modifications have been actively utilized as the signal amplifiying nanoplarforms for fabrication of electrochemical receptor based biosensors. In particular, nanomaterials such as noble metal nanoparticles (Au, Pt) [27, 55], carbon based nanostructures [56, 57], magnetic nanoparticles (MNPs) [19, 58], quantum dots (QDs) [59, 60], metal oxide nanoparticles [61, 62] and polymer nanomaterials [63, 64] have been attracted a lot of attention in this field.

Within the group of carbon nanostructures, graphene and its derivatives are considered as the rapidly "rising star" carbon nanomaterials due to tailorable chemical functionalities originated from the pristine sp^2 hybridization, superior mechanical strength, good chemical and thermal stabilities, low density, excellent thermal conductivities and low toxicity [65]. Graphene oxide (GO) well-known for its distinct physiochemical properties and a high quantity of oxygen-containing functional groups is electrically semiconducting and has low electronic conductivity. In some cases, it is necessary to regain graphene's desirable characteristics such as electrical conductivity or catalytic activity. Reduced graphene oxide (rGO) with higher electrical conductivity than GO still contains some oxygen related functional groups which can bind to the biological probes [66]. Graphene quantum dots (GQDs), as the newest member of graphene family, are graphene sheets with lateral size smaller than 100 nm in single, double and multiple layers, and diameters spanning the range 3–20 nm mainly [25, 67]. They combine the advantages of graphene with the quantum confinement of carbon dots for electrochemical biosensing applications.

Nanomaterials as the signal generating probes

Growing demand for developing ultrasensitive electrochemical bioassays has led to the design of numerous signal amplification strategies based on nanoparticle electroactive labels. The importance of the use of nanomaterials as the signal tags for amplification of electrochemical responses has been reflected in the number of reviews published on this topic [68]. Nanoparticles consist of thousands of atoms, which in principle can be oxidized or reduced electrochemically. Consequently, when all bioreceptor molecules are labeled with nanoparticles, the loading of electroactive species on the electrode surface significantly increases, which leads to enhanced sensitivity of the biosensor. Nanoparticles of Au [69, 70] and Ag [71, 72] have been used for this purpose. AuNPs can be electrochemically oxidized in HCl to produce electroactive $AuCl_4^-$, which is then reduced to give a detectable signal. Conjugated metal sulfide nanoparticles, such as CdS [73], PbS [74] and ZnS [75], have also been extensively used as labels in the development of ultrasensitive electrochemical affinity bioassays. These metal sulfides are easily dissolved in HNO_3 medium to obtain Cd^{2+}, Pb^{2+} and Zn^{2+}, which can then be detected with high sensitivity using stripping voltammetry.

Nanomaterials as the carriers for signal tags in label-free sandwich detection strategies

Along with the use of nanomaterials for the construction of nanostructured electrode surfaces, their utilization as carriers of signal tags for electrochemical signal amplification is another less widespread but equally relevant application. Nanomaterials, especially carbon nanostructures, have been demonstrated to be excellent carriers

for signal probes with their good conductivity and biocompatibility in label-free electrochemical sandwich-type biosensors. Nanoscale materials have a greater surface area, which increases the amount of the accumulation of redox probes, which can be led to high sensitivity. Typically, graphene and its derivatives are the promising supports for immobilization of redox tags such as thionine or methylene blue [76]. The graphene nanosheets offer a large surface area for immobilization of electroactive compounds as the electrochemical signal probes. In addition, the high electrical conductance is a distinctive character for graphene, which leads to increased current density and high sensitivity. Our group developed a sandwich-type electrochemical aptasensor for detection of MUC 1 in breast cancer patients [77]. In this work, rGO-N'^{1},N'^{3} dihydroxymalonimidamide nanosheets with large surface area, excellent electroconductivity and good adsorption capacity were employed, not only as an ideal carrier to immobilize numerous secondary aptamers, but also as a suitable sorbent for the accumulation of electroactive thionine. Another example of these nanocarries is core-shell nanocomposites. Valipour and Roushani [78] reported an electrochemical sandwich-type immunoassay for the core antigen of hepatitis C based on a nafion coated TiO_2 nanocomposite as the carrier of Celestine Blue tags.

Candidate metabolic biomarkers for diagnosis of diseases

Metabolomics, a postgenomic approach used to rapidly identify global metabolic changes in biological systems, has been increasingly applied to diagnosis of diseases, measurement of the response to treatment, discovery of biomarkers and identification of perturbed pathways. In this review, we attempted to explore the electrochemical biosensing strategies for the potential biomarkers related to some diseases and for validation of these biomarkers as predictors to diagnose the neurodegenerative diseases, autism spectrum disorder diseases and hepatitis.

Neurodegenerative diseases

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS) are incurable and debilitating conditions that result in progressive degeneration and death of nerve cells. Currently, the human and animal studies are developing new and compelling ideas about the early diagnosis of these disorders, with the goal of slowing or stopping their progression. These efforts reveal the presence of abnormal metabolites in many degenerative diseases that interfere with normal cellular functions. The ultrasensitive assessment of these functional biomarkers for neurodegenerative diseases is important in diagnosis, management and treatment of these disorders. Considering the studies performed in the previous decade, 101 metabolites have been identified as putative biomarkers for AD, PD and ALS. Notably, alanine, choline, creatinine, creatine and uric acid are the shared metabolite signatures among these three diseases [6, 7]. Thus, a variety of electrochemical biosensors based on enzymatic reacrions have been developed for the selective and sensitive determination of these metabolic biomarkers. In the most of these cases, the measurement is based on the amperometric detection of hydrogen peroxide (H_2O_2), as a side product of the choline oxidase catalysed reaction.

Alanine

D-amino acid oxidase (DAAO) as a peroxisomal enzyme has been used in several biosensors for the determination of the *D*-amino acids such *D*-alanine in biological fluids. As seen in Table 1, with combination of excellent electron transfer ability of CNTs and high bioactivity of DAAO, various signal amplification biosensors for assessment of *D*-alanine have been designed [79–83]. The high sensitivity and selectivity of these catalytic biosensors indicate the good conductivity of designed nanoplatforms and successful maintenance of DAAO bioactivity.

Choline

Choline is a precursor of the neurotransmitter acetylcholine, one of the crucial brain chemicals involved in memory. Individuals suffer from various nerve disorders such as PD and AD due to the lack of acetylcholine [84]. The quantitative determination of choline is important in clinical analysis, especially in the early diagnosis of brain disorders. Among different methods available for choline detection, the electrochemical biosensors based on choline oxidase (ChO) and nanomaterials present advantages such as simplicity, reliability, high sensitivity and selectivity. A broad range of the electrochemical biosensors for determination of choline using the electrocatalytic properties of conductive nanomaterials and enzymatic activity of ChO has been listed in Table 2 [85–111].

Creatinine and creatine

Creatinine is the end product of creatine catabolism in mammals [112]. It is found together with creatine in muscle tissue and in blood. Determination of these metabolic biomarkers in biological fluids is essential for

Table 1 A list of nanomaterials-based biosensors for electrochemical detection of *D*-alanine

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
D-Alanine	GCE/MWCNT/Au nanofilm/DAAO/Sol-gel film	20 nM	0.25–4.5 μM	[79]
	GCE/MWCNTs/Au-Pt NPs/DAAO	1.67 nM	5 nM–5 mM	[80]
	GCE/MWCNTs/PTCA/DAAO	3.3 nM	10 nM–1 mM	[81]
	GE/PANI/Cu NPs/c-MWCNTs/DAAO	0.2 μM	1–700 μM	[82]
	SPE/CNTs/PB/DAAO	-----	5–200 μM	[83]

GCE,Glassy carbon electrode; MWCNT, Multiwall carbon nanotube; DAAO, D-Amino acid oxidase; PTCA, 3,4,9,10-Perylene tetracarboxylic acid; GE, Gold electrode; PANI, Polyaniline; SPE, Screen printed electrode; PB, Prussian blue

detection of neurodegenerative diseases. For this purpose, the commercial enzymes containing creatininase (CA), creatinase (CI) or sarcosine oxidase (SO) immobilized on the nanomaterial modified electrodes have been extensively used as the biosensing interfaces. Table 3 represents the recent developments in design and fabrication of electrochemical biosensors for the determination of creatine [113] and creatinine [114–120].

Table 2 A list of nanomaterials-based biosensors for electrochemical detection of choline

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
Choline	GCE/Chitosan-MWCNT/$(AuNPs)_4$/ChO	0.6 μM	3–120 μM	[85]
	GCE/MnO_2 NPs/ChO/Nafion	5 μM	8.0 μM–1.0 mM	[86]
	AuSPE/Silica film-ChO	6 μM	0.02–0.6 mM	[87]
	GE/TGA-SAM/ChO μ-chip	0.012 nM	0.05 nM–10.0 μM	[88]
	Pyrolytic graphite/ZnO/MWCNTs/ChO-AChE/PDDA	0.3 μM	1–800 μM	[89]
	CPE/PANI/SiO_2/ChO	0.1 μM	0.5–10 μM	[90]
	GCE/BG/PB-Ni/ChO	0.45 μM	0.45–100 μM	[91]
	GCE/Chitosan-AuNPs-G/Fe_3O_4-TiO_2@NH_2-ChO	1 nM	3 nM–1.12 mM	[92]
	GE/PBBIns-G-ChO	0.02 μM	0.1–830 μM	[93]
	GCE/Fc-rGO/HRP/ChO	0.35 μM	1–400 μM	[94]
	GCE/ZrO_2NPs/MWCNTs/AChE-ChO	0.01 μM	0.05–200 μM	[95]
	GCE/NH_2-MWCNT/RTIL/ChO	2.7 μM	0.69 pM–0.67 mM	[96]
	Graphite electrode/Poly(TBT_6–NH_2)/GA/ChO	16.8 μM	0.1–10 mM	[97]
	GCE/PB-$FePO_4$ nanostructures/PDDA-ChO	0.4 μM	2 μM–3.2 mM	[98]
	CPE/ChO	-----	0.1–500 μM	[99]
	PtE/Chitosan-MWCNT/MPTMOS Sol/AuNPs-ChO	15 μM	0.05–0.8 mM	[100]
	GE/Cystamine/GA/Chitosan-Fe_3O_4 NPs/GA/ChO	0.1 nM	1 nM–10 mM	[101]
	PtE/CNT/$K_3Fe(CN)_6$/ChO	12.1 nM	0.1 μM–4 mM	[102]
	PtE/MWCNTs-AuNPs/PDDA-ChO	0.3 μM	0.001–0.5 mM	[103]
	PIGE/MWCNT-CdS QDs/ChO	0.8 μM	1.7–332.0 μM	[104]
	PtE/Au nanorods/ChOx/PVA	10 μM	20 μM–0.4 mM	[105]
	GCE/Chitosan/α-MnO_2 NPs/ChO	1.0 μM	2.0 μM–0.58 mM	[106]
	GCE/Chitosan/β-MnO_2 nanowires/ChO	0.3 μM	1.0 μM–0.79 mM	
	GCE/MnO_2 NPs/Chitosan-ChO	-----	10 μM–2.1 mM	[107]
	PtE/MWCNT/SiO_2 sol-gel-ChO	0.5 μM	5 μM–0.1 mM	[108]
	PtE/MWCNT/Sol-gel silicate-ChO	0.1 μM	5 μM–0.1 mM	[109]
	GCE/CNT/HRP/ChO	10 μM	50 μM–5 mM	[110]
	GCE/{MWNTs/PANI}$_5$/{PANI}$_3$/ChO	0.1 μM	1 μM–2 mM	[111]

GCE, Glassy carbon electrode; GE, Gold electrode; CPE, Carbon paste electrode; SPE, Screen printed electrode; G, Graphene; r-GO, Reduced graphene oxide; Fc, Ferrocene; MWCNT, Multiwall carbon nanotube; PB, Prussian blue; ChO, Choline oxidase; AChE, Acetylcholinesterase; PVA, Polyvinyl alcohol; PANI, Polyaniline; Poly(TBT_6–NH_2), Poly(6-(4,7-di(thiophen-2-yl)-2H-benzo[d][1,2,3]triazol-2-yl)hexan-1-amine); MPTMOS, (3-Mercaptopropyl) trimethoxy silane; HRP, Horseradish peroxidase; GA, Glutaraldehyde; RTIL, Room temperature ion liquid; BG, Bucky gels; PBBIns, Poly(N-butyl benzimidazole)

Table 3 A list of nanomaterials-based biosensors for electrochemical detection of creatine and creatinine

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
Creatine	Fe_3O_4-CPEE (CI or SO)	0.2 μM	0.2–3.8 μM 0.9–0.12 mM	[113]
Creatinine	GCE/CA NPs/CI NPs/SO NPs	0.01 μM	0.01–12 μM	[114]
	Teflon/MWCNT/AuNPs/FC/HRP/CA or CI or SO	0.1 μM	0.003–1.0 mM	[115]
	FC-SPE/Creatinine amidinohydrolase	2.4 μM	5–1000 μM	[116]
	PtE/g-PANI/Chitosan/Fe_3O_4 NPs/CA or CI or SO	1 μM	1–800 μM	[117]
	Gold chip-PPy-Creatinine/Ab-HRP	0.46 mg dL^{-1}	Up to 11.33 mg dL^{-1}	[118]
	PtE/PANI/Carboxylated MWCNT/CA or CI or SO	0.1 μM	10–750 μM	[119]
	PtE/PANI/MWCNT/Chitosan/ZnO NPs/CA or CI or SO	0.5 μM	10–650 μM	[120]

GCE, Glassy carbon electrode; GE, Gold electrode; CPEE, Carbon paste enzyme electrode; SPE, Screen printed electrode; Fc, Ferrocene; MWCNT, Multiwall carbon nanotube; CA, Creatininase; CI, Creatinase; SO, Sarcosine oxidase; PANI, Polyaniline; g-PANI, Graft-polyaniline; HRP, Horseradish peroxidase; PPy, Polypyrrole

Uric acid

Uric Acid (UA), considered as a waste of cellular metabolism, has now received increasing attention because it was found to directly participate in the pathogenesis of many human diseases including neurological disorders. UA protects neurons in neurodegenerative disorders via antioxidative effects. Fast and accurate determination of UA in human physiological fluids has been recognized as a vital clinical test in the diagnosis of patients suffering from numerous metabolic disorders. Thus, continuous monitoring of UA levels in the blood is of paramount importance. The important challenge in the electrochemical detection of UA is the co-existence of many interfering compounds in biological systems such as dopamine (DA) and ascorbic acid (AA). To overcome this limitition, non-enzymatic sensing strategies have been designed using the materials with high electrocatalytic activity to oxidation of UA [121–136]. These nanocomposites electrocatalytically oxidize UA, DA and AA at different potentials, so that the simultaneous determination of the analytes by these sensors will be in rich. Although these sensors can effectively achieve UA detection, there is a scope for improvement in the receptor based biosensors. The binding of UA to the active site of uricase enzyme is a very specific and strong interaction. Thus, considerable efforts have been focused on the development of new enzyme-based biosensors. Table 4 presents a list of the electrochemical enzymatic biosensors for evaluation of UA in biological fluids [137–175].

Autism Spectrum Disorder

The pattern of behavioral symptoms now described as Autism Spectrum Disorder (ASD) was first recognized in 1943 [176]. ASD is a complex neurodevelopmental condition that occurs within the first 3 years of life, which is marked by social skills and communication deficits along with stereotyped repetitive behavior [177]. The prevalence of autism has been increased by more than tenfold in the last decade. This growing prevalence has stimulated intense research into the identification of biochemical markers related to autism would be advantageous for earlier clinical diagnosis and intervention.

The etiology of this developmental disorder is poorly understood, and no biomarker has definitely been identified. However, many investigators are addressing the concept of autism as a general metabolic disorder. Some studies suggest that oxidative stress-induced mechanisms and reduced antioxidant defense, mitochondrial dysfunction and impaired energy metabolism (nicotinamide adenine dinucleotide (NAD), adenosine triphosphate (ATP), pyruvate) and altered tryptophan metabolism are major causes of ASD [178–180]. They have shown a disturbance in energy metabolism in the brains of autistic children with a marked increase in the size especially in areas related to social cognitive processes. In addition, tryptophan is a precursor of important compounds, such as serotonin, quinolinic acid and kynurenic acid, which are involved in neurodevelopment and synaptogenesis. The decreased tryptophan metabolism may alter brain development, neuroimmune activity and mitochondrial function [181].

These findings provided initial support for the possibility that the evaluation strategies of biomarkers may be effective for a broad range of individuals with ASD. Thus, a variety of biosensors have been developed for blood analysis of these children. Table 5 provides renewed insight related to electrochemical biosensors for ultrasensitive detection of ASD metabolic biomarkers [61, 182–233].

It should be noted that most of these electrochemical biosensors have been fabricated based on the formation

Table 4 A list of nanomaterials-based biosensors for electrochemical detection of uric acid

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
Uric acid (UA)	ITO/ZnS NPs/UOx/Nafion	1.79 μM	0.01–1.5 mM	[137]
	ITO/ZnS nanoflakes /UOx/Nafion	1.51 μM	0.01–2.0 mM	
	ITO/ZnS urchin-like nanostructures/UOx/Nafion	0.7 μM	0.01–1.7 mM	
	AgE/ZnO nanorods/UOx/Nafion	5 nM	0.01–4.56 mM	[138]
	GCE/PB/Poly(4-ASA)/UOx	3.0 μM	10–200 μM	[139]
	p-n junction heterostructure/ZnO/CuO/UOx	5.45 μM	50 μM–1 mM	[140]
	GCE/GO-UOx	3.45 μM	0.02–0.49 mM	[141]
	CuE/Au/*L*-methionine/UOx	2.4 μM	-----	[142]
	(Ag/Si) electrode/ZnO nanosheets/UOx/Nafion	0.019 μM	0.05–2.0 mM	[143]
	GCE/PVF/Gelatin/MWCNT/UOx	23 nM	0.2 μM–0.71 mM	[144]
	GCE/Fc/UOx/Nafion	230 nM	500 nM–600 μM	[145]
	GE/MWCNT/Plated Pd/PdNPs-PFBA-UOx/Chitosan	0.1 μM	1.0 μM–2.5 mM	[146]
	ITO/NiO/Ni/UOx	0.03 mM	0.05–1 mM	[147]
	PtE/Chitosan-g-PANI/Fe_3O_4 NPs/UOx	0.1 μM	0.1–800 μM	[148]
	GE/Ag NPs/Chitosan-CNTs nanofiber/UOx	1.0 μM	1–400 μM	[149]
	GE/Pt_{nano}-PTBA-UOx/Chitosan	1 μM	5 μM–1.2 mM	[150]
	ITO/ZnO:Nitrogen nanocrystal/UOx	0.04 mM	0.05–1.0 mM	[151]
	GE/AuNPs/Amino acid/UOx	7.0 μM	0.02–2.5 mM	[152]
	GE/ZnO nanowires/UOx/Nafion	25.6 μM	100–590 μM	[153]
	SPE/FC-GO/UOx	0.1 μM	1–20 μM	[154]
	SPE/PB/UOx	0.01 mM	0.03–0.3 mM	[155]
	ITO-μEA/APTES/BS/UOx	0.0084 mM	0.058–0.71 mM	[156]
	PtE/PPy/UOx	75 pM	75 pM–8.3 μM	[157]
	GE/*T*-ZnO_{nano}/UOx/Nafion	0.8 μM	0.8 μM–3.49 mM	[158]
	SPE/CoPC/CA/UOx/PC	15 μM	15 μM –0.25 mM	[159]
	GE/PANI/MWCNTs/PB NPs/Chitosan-GA/UOx	5 μM	0.005–0.8 mM	[160]
	Glass(Au)/ZnO nanoflakes/Nafion/UOx	0.5 μM	0.5–1500 μM	[161]
	ITO/APTES/AuNP/MUA-MPA/UOx	54 μM	0.07–0.63 mM	[162]
	Glass(Au)/ZnO nanotubes/UOx	500 nM	500 nM–1500 μM	[163]
	Plastic(Au)/ZnO nanowires/UOx	1 μM	1–650 μM	[164]
	Plastic(Au)/ZnO nanowires/Nafion/UOx		1–1000 μM	
	Glass/Ti/Pt/NiO/UOx	0.11 mM	0.05–1.0 mM	[165]
	GE/MPTS-Sol/UOx/PtNPs	0.1 nM	Up to 1.4 mM	[166]
	GE/MWCNT/AuNPs/UOx	0.01 mM	0.01–0.8 mM	[167]
	ITO/APTES/Bis[sulfosuccinimidyl]/UOx	0.037 mM	0.05–0.58 mM	[168]
	ITO/PANI/MWCNT/Bacillus UOx	5 μM	0.005–0.6 mM	[169]
	GCE/TiO_2 nanotube/UOx	1 μM	1 μM–5 mM	[170]
	PGE/MWCNT/ZnO NPs/UOx/PDDA	2 μM	0.05–1 mM	[171]
	Pt plate/PANI-PPy/UOx	1.0 μM	2.5 μM–85 mM	[172]
	Ir-C electrode/UOx	10 μM	0.1–0.8 mM	[173]
	GE/Cysteine/ZnS QDs/UOx	2 μM	0.05–2 mM	[174]
	PtE/PPy-UOx	0.5 μM	0.5 μM–1 mM	[175]

GCE, Glassy carbon electrode; GE, Gold electrode; CPEE, Carbon paste enzyme electrode; SPE, Screen printed electrode; UOx, Uricase; MWCNT, Multiwall carbon nanotube; PANI, Polyaniline; PB, Prussian blue; Ir–C, Ir-modified carbon; PVA, Polyvinyl alcohol; PVF, Poly(vinylferrocene); TGA, Thioglycolic acide; MUA, 11-Mercapto undecanoic acid; MPA, 3-Mercapto propionic acid; SAM, Self-assembled monolayer; PTBA, Poly(thiophene-3-boronic acid); PC, Polycarbonate; CoPC, Cobalt phthalocyanine; CA, Cellulose acetate; PDDA, Poly(diallyldimethyl ammonium chloride); *T*-ZnO, Tetrapod-shaped ZnO; PGE, Pencil graphite electrode; PIGE, Paraffin impregnated graphite electrode; Fc, Ferrocene; HRP, Horseradish peroxidase; VACNT, Vertically aligned CNT; IL, Ion liquid; g-PANI, Graft-polyaniline; PFBA, Poly(furan-3-boronic acid); ITO-μEA, Indium tin oxide microelectrode array; 4-ASA, 4-Amino-salicylic acid; APTES, 3-Aminopropyltriethoxysilane; BS, Bis[sulfosuccinimidyl]suberate; MPTMOS, (3-Mercaptopropyl) trimethoxy silane; PPy, Polypyrrole

Table 5 A list of nanomaterials-based biosensors for electrochemical detection of metabolite biomarkers for autism spectrum disorder

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
Adenosine triphosphate (ATP)	GCE/Nafion-TGA caped CdTe QDs/DNA/Aptamer/Methylene blue	45 pM	0.1 nM–1.6 μM	[60]
	GE/AuNPs/Aptamer/Peptide	0.1 pM	0.1 pM–5 nM	[182]
	GE/Hairpin aptamer 1/ssDNA/ Hairpin aptamer 2-Methylene blue	0.6 nM	1–200 nM	[183]
	GE/Fc-aptamer/ssDNA/Methylene blue	90.8 pM	0.1 nM–100 μM	[184]
	GE/Dendritic aptamer-DNA nanoassembly/ST-AP/α-NP	5.8 nM	10 nM-10 μM	[185]
	Nanogap electrode/Polysilicon/Aptamer	10 nM	10–100 nM	[186]
	GE/Nano-organic framework-Ce/Aptamer	5.6 nM	10 nM–1 mM	[187]
	SPE/AuNPs/Aptamer fragment (F_1)/AgNPs-GO/Aptamer fragment (F_2)	5.0 nM	10–850 nM	[188]
	GCE/PDA/PEG/Aptamer	0.1 pM	0.1−1000 pM	[189]
	GE/DNA-Methylene blue/Hairpin aptamer/ATP/Nb.BbvCI	3.4 nM	10 nM−1 μM	[190]
	GE/DTT/Aptamer/c-DNA-Methylene Blue	1.4 nM	5 nM–1 μM	[191]
	GE/Aptamer/Hemin-GO	0.08 nM	0.5–100 nM	[192]
	GCE/MoS_2 nanosheets-AuNPs/Aptamer/MB	0.74 nM	1 nM–10 mM	[193]
	SPE/MnO_2 nanosheet/Fc-aptamer	0.32 nM	0.5–500 nM	[194]
	GE/Beacon like DNA	20 pM	100 pM–1 nM	[195]
	GE/c-DNA/Trigger aptamer duplex DNA-Aptamer/ATP/Haipin 1-Haipin 2/Silver nanotag	30 fM	0.1 pM–100 nM	[196]
	GCE/AuNPs/Aptamer/$Ru(bpy)_3^{2+}$/GO	4.8 pM (ECL) 6.7 pM (EIS)	10 pM–10 nM	[197]
	GCE/Au-G nanosheets/Thionine/DNA/Aptamer-PdCu@MWCNT/HRP/GOx	2.5 nM	10–400 nM	[198]
	GCE/NH_2-G/AuNPs/Aptamer	10 pM	10 pM–100 nM	[199]
	GE/Thiolated DNA/DNA-methylene blue/DNA1/DNA2/DNA ligase/C-DNA/Invasive DNA/Zn^{2+}	0.05 nM	0.1–1000 nM	[200]
	GCE/GO-PANI/Aptamer1/ATP/Aptamer2-PNN@ CdS QDs	0.1 pM	0.5 pM–20 nM	[201]
	GE/PBTA-CCG-Aptamer 1/ATP/Fe_3O_4-Aptamer 2/ADA	13.6 nM	Up to 1 μM	[202]
	GCE/NPG/Ru-silica/ssDNA 1/ATP/Fc-SSDNA 2	0.03 pM	0.1 pM–10.0 nM	[203]
	GCE/Aptamer/Tris(bpyRu)-β-CD	0.01 nM	10.0–0.05 nM	[204]
	GCE/MWCNT/IL/Chitosan/ssDNA/PtNPs@Aptamer	1 nM	1–750 nM	[205]
	GCE/CdTe QDs-DNA 1/Aptamer/ATP/DNA 2-AuNP/DNAzyme	7.6 nM	8−2000 nM	[206]
	GE/Aptamer fragment 1/Aptamer fragment 2/Auxiliary probe 1/Auxiliary probe 2/Auxiliary probe 3/RuHex	20 fM	20 fM−10 nM	[207]
	GCE/PoPD/G/Aptamer-Methylene blue	0.3 nM	10 nM–2 mM	[208]
	GE/ssDNA1/ATP/ssDNA2-SiO_2-GQD	1.5 pM	5 pM–5 mM	[209]
	Nanoporous GE/Aptamer	100 nM	Up to 3 mM	[210]
	ITO/Hairpin aptamer (Exonuclease III-assisted target recycling strategy)	0.1 nM	1–20 nM	[211]
	CPE/AuNP/G/Aptamer-FAD	11.4 pM–30 μM	20.1 pM	[212]
	GE/Aptamer-Methylene blue/ssDNA-Fc	1.9 nM	10 nM–100 μM	[213]
	GE/MPA/Amino-DNA segment1/ATP/ DNA segment2-AgNPs	1 mM	-----	[214]
	GCE/T(4-Mop)PS_4-G/Aptamer	0.7 nM	2.2 nM–1.3 μM	[215]
	GE/G/Aptamer	15 nM	15 nM–4 mM	[216]
	Nitrogen doped TiO_2 nanotubes electrode/Aptamer/ATP/Fe_3O_4-CdTe-COOH-ssDNA/bbcDNA	10 nM	10 nM–1.0 mM	[217]
	GE/Aptamer1/ATP/Aptamer2-RuSiNP	0.2 pM	1 nM–1 pM	[218]
	GE/Aptamer-PbS or CdS QDs	30 nM	-----	[219]
	GE/$Ru(bpy)_3^{2+}$-AuNPs/FC-aptamer/ssDNA	5 nM	10 nM–0.1 μM	[220]
	GE/Aptamer/ATP/c-DNA/Avidin-QDs	6 nM	0.018–90.72 μM	[221]
	GE/DNA1/DNA2/AuNPs-DNA3/$Ru(NH3)_6^{3+}$	0.02 nM	0.02–3 nM	[222]
	GE/Anchored DNA/Target-responsive DNA/Reporter DNA capped AuNPs	0.2 nM	1 nM–10 μM	[223]
	GCE/Chitosan/Nano-MnO_2/Aptamer	0.8 nM	1–100 nM	[224]
	GE/HDT/AuNPs/Aptamer/Methylene blue	1 nM	5–1000 nM	[225]

Table 5 (continued)

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
	GE/AuNPs/DNA1/DNA2@AuNPs-Linker DNA/$Ru(NH3)_6^{3+}$	0.18 nM	0.5–4.0 nM	[226]
NADH	GE/G-DNA tetrahedron-AuNPs	1 fM	1 fM–10 pM	[227]
	GE/AuNPs/PSSG/$Ru(bpy)_3^{2+}$/ADH	1 nM	2.5 nM–586 μM	[228]
Pyruvate	CFE/Poly(neutral red)/PyOx	34 μM	90–600 μM	[229]
Tryptophan	SPE/NH_2-FSN/AuNPs/Aptamer/Hemin	0.026 nM (DPV) 0.01 nM (EIS)	0.06–250 nM	[230]
	AuSPE/MWCNT/Aptamer	4.9 pM	10 pM–0.1 mM	[231]
	GE/MWCNT/Aptamer	0.064 nM	0.0001–10 μM 10–300 μM	[232]
	ITO/APTES/GO/HSA	-----	0.10–1.0 mM	[233]

GE, Gold electrode; SPE, Screen printed electrode; GCE, Glassy carbon electrode; G, Graphene; CPE, Carbon paste electrode; CFE, Carbon film electrode; ITO, Indium tin oxide; PDA, Polydopamine; PEG, Polyethylene glycol; FC, Ferrocene; PBTA, 1-pyrene butyric acid; CCG, Chemically converted graphene; ST-AP, Streptavidin-alkaline phosphatase; MPA, 3-Mercaptopropionic acid; ADA, Adenosine deaminase; GQD, Graphene quantum dot; PNN, Platinum nanostructured network; NPG, Nanoporous gold; Ru-silica, $Ru(bpy)_3^{2+}$-doped silica; Tris(bpyRu)-β-CD, Tris(bipyridine)ruthenium(II)-β-cyclodextrin[tris(bpyRu)-β-CD]; PoPD, Poly(o-phenylenediamine); T(4-Mop)PS_4, meso-Terakis(4-methoxyl-3-sulfonatophenyl) porphyrin; DTT, Dithiothreitol; RuHex, Hexaammineruthenium(III); FSN, Functionalized silica nanoparticle; IL, Ion liquid; QDs, Quantom dots; FAD, Flavin adenine dinucleotide; MWCNT, Multi-wall carbon nanotube; PyOx, Pyruvate oxidase; APTES, 3-Aminopropyl triethoxysilane

of aptamer-target complexes. The DNA aptamer for adenosine is one of the most studied since the initial report in 1995 by Huizenga and Szostak [234]. It has a similar affinity to a few adenosine derivatives including adenosine monophosphate (AMP), cyclic adenosine monophosphate (cAMP) and ATP, but it cannot bind other nucleosides such as guanosine [235].

Tryptophan aptamers with different dissociation constants have been extensively studied for the affinity based bioassays [236]. The investigation of specificity showed that these aptamers strongly bind to tryptophan and possess almost no binding to other amino acids, so that they can be used as the efficient biorecognition tools for biosensing applications.

Hepatitis

Hepatitis refers to an inflammatory condition of the liver. It may be caused by viruses, drugs or alcohol, although the most common cause is viruses. Viral hepatitis can be caused by five hepatitis viruses including A, B, C, D and E. During a five-year period, 10–20% of chronic hepatitis leads to cirrhosis [237]. Accordingly, the major clinical risk factor for hepatocellular carcinoma (HCC) development is liver cirrhosis as 70–90% of HCCs develop in a cirrhotic liver [238]. These data clearly indicate the critical importance of early diagnosis of hepatitis. Therefore, the reliable and noninvasive diagnostic methods to predict and assess liver hepatitis are needed. The blood testing including enzyme immunoassay, polymerase chain reaction (PCR) assay, recombinant immunoblot assay, biomarker assay and quantification of hepatitis RNA in serum are the most common methods for detection of hepatitis. Among these, the analysis of metabolic biomarkers is a powerful strategy to advance the diagnosis, treatment and prevention of hepatitis.

Liver is a major metabolic organ and its infection is expected to result in measurable changes in such metabolite levels as tryptophan, phenylalanine, histidine, tyrosine, ethanol, lactic acid, *L*-proline and fumaric acid [239]. Especially, the concentration of amino acids is very often found altered in liver diseases [240]. The high blood level of lactate also plays an important role in liver dysfunction [241]. Both acute and chronic hepatic diseases can result in lactate accumulation and lactic acidosis. In addition, several studuies reported the relationship between blood alcohol concentration and hepatic enzymes in these patients [242]. Hepatic enzymes can be used as a predictor of hepatic injury.

A variety of electrochemical biosensing methods have been developed to detect metabolic biomarkers for the fast diagnosis of hepatitis. Most of these biosensors have been designed based on the amperometric determination of H_2O_2, a by-product of the enzyme reactions. They reveal good performances such as increased sensitivity, excellent selectivity and good repeatability, when compared with non-enzymatic biosensors [243, 244]. Table 6 summarizes a list of reported electrochemical biosensors based on the biorecognition elements for ultrasensitive detection of hepatitis metabolic biomarkers [228, 230–234, 245–340]. The analytical characteristics of these biosensors confirm that they can serve as potential devices for the detection of metabolism dysregulations in patients with hepatitis.

Table 6 A list of nanomaterials-based biosensors for electrochemical detection of metabolite biomarkers for hepatitis

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
Tryptophan	SPE/NH_2-FSN/AuNPs/Aptamer/Hemin	0.026 nM (DPV) 0.01 nM (EIS)	0.06–250 nM	[230]
	AuSPE/MWCNT/Aptamer	4.9 pM	10 pM–0.1 mM	[231]
	GE/MWCNT/Aptamer	0.064 nM	0.0001–10 μM 10–300 μM	[232]
	ITO/APTES/GO/HSA	-----	0.10–1.0 mM	[234]
Alcohol	GE/AuNPs/PSSG/$Ru(bpy)_3^{2+}$/ADH	12 nM	5.0 μM–5.2 mM	[228]
	GCE/Fe_3O_4/PDA/AOx	130 μM	Up to 3.0 mM	[245]
	GCE/MnO_x-MoO_x/PtNPs/Gluconobacter oxydans biofilm	-----	0.075–5.0 mM	[246]
	SPE/MWCNT/AuNPs/PNR/ADH/GA	96.1 μM	320.2–1000 μM	[247]
	GCE/Chitosan/Nafion/AOx-AuNPs/PANI	7 μM	10 μM–4.7 mM	[248]
	SPE/AA/TO-AuNPs/ADH/Chitosan	0.14 μM	1 μM –2.0 mM	[249]
	GCE/G-CdS QDs/IL/CPZ-SO/ADH	-----	-----	[250]
	Graphite electrode/Poly(BIPN)/COOH-MWCNT/AOx	0.17 μM	0.855–11.97 mM	[251]
	GCE/MWCNT/Nafion/HRP/Sol-gel chitosan/FcAOx	2.3 μM	5 μM–3 mM	[252]
	GCE/NiOxNPs/ADH-Nafion	6.4 μM	0.2–6 mM	[253]
	GE/MWCNT-Nafion/AOx-PEI	5 μM	8–42 μM	[254]
	GCE/$Ru(bpy)_3^{2+}$–G/BSA/ADH	0.1 μM	1–2000 μM	[255]
	GCE/G-AuNPs/ADH	1.5 μM	5–377 μM	[256]
	GCE/CNT/Chitosan-NAD+-ADH	8–30 μM	Up to 20 mM	[257]
	GE/Cysteine/TTF/AOx	30 μM	0.1–1.0 mM	[258]
	GCE/NH_2-$Ru(bpy)_3^{2+}$-doped silica NPs/ADH	50 nM	0.1 μM–10 mM	[259]
	GCE/SWCNT/PBCB/ADH	0.1 mM	0.4–2.4 mM	[260]
	GCE/OMC/Meldola's Blue-ADH	19.1 μM	Up to 6 mM	[261]
	GCE/MWCNT-Chitosan-ADH	0.52 μM	-----	[262]
	CFE/MWCNT/AOx	86 μM	Up to 1.4 mM	[263]
	SPE/Nafion-AuNPs-ADH-Meldola's blue	16 μM	8.3 mM	[264]
	Teflon electrode/MWCNT/Au_{Coll}/ADH Teflon electrode/MWCNT/ADH	4.7 μM 32 μM	0.02–1.0 mM 0.010–1.0 mM	[265]
	GCE/Nafion-TiO_2 sol gel-CNT-ADH	5.0 μM	Up to 3 mM	[266]
	GCE/SWCNT/Poly(nile blue A)-ADH	50 μM	0.1–3.0 mM	[267]
	GCE/SWCNTs-PDDA-ADH/Nafion	90 μM	0.5–5.0 mM	[268]
	GCE/PVA–MWCNT–ADH	13 μM	Up to 1.5 mM	[269]
	ITO/AuNPs-$Ru(bpy)_3^{2+}$-ADH	3.33 μM	10 μM–10 mM	[270]
	GCE/PTH-CNF/AOx	1.7 μM	2.0–252 μM	[271]
	GCE/MWCNTs-Nafion-ADH	3 μM	Up to 0.1 mM	[272]
	GE/PPY_{Ox}/AOx-GA-BSA	2.3 μM	Up to 0.75 mM	[273]
	CPE-MWCNT- Meldola's Blue-ADH	5 μM	0.05–10 mM	[274]
	Graphite rods/HRP/EDP-Os complex/EDP-AOx	-----	Up to 2 mM	[275]
Fumaric acid	Pt/SU-8 photoresist/Fumarate hydratase	0.026 mM	0.1–3.0 mM	[276]
Histidine	GCE/G-AuNPs/DNAzymes	0.1 pM	10 pM–10 μM	[277]
	GE/HDT/AuNPs/DNA1-DNA2-FC	0.1 pM	10 pM–50 nM	[278]
	GE/HDT/DNA1-DNA2-FC	1 nM	1 nM–10 μM	
Lactic acid or Lactate	PET/Cu foil/G nanowalls/LOx	1.0 μM	1.0 μM–10.0 mM	[279]
	SPE/Glycerol/NAD^+/BSA/PyrOx-LDH	17 μM (R_{IM}) 20 μM (CPE_{IM})	0.01–0.25 mM	[280]
	PEG/PANI-CuNPs-MWCNT/LOx	0.25 μM	1.0–2500 μM	[281]
	SPE/LOx/BSA/HRP/Chitosan/FcMe/MWCNT	22.6 μM	30.4–243.9 μM	[282]
	GCE/$FcMe_2$-LPEI/LOx	3 μM	Up to 5 mM	[283]
	SPE/PB nanocubes/LOx	10 μM	0.01–0.5 mM	[284]
	CPE-Fe_3O_4-PB/LOx	0.59 μM	7.5 μM–0.13 mM	[285]

Table 6 (continued)

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
	SPE/GO/$K_3[Fe(CN)_6]$/LOx	60 μM	0.5–15 mM	[286]
	GE/MPTS/DNP/LOx	16 μM	0.053–1.6 mM	[287]
	GCE/PPy-F127 NPs/LOx/Nafion	0.0088 mM	0.015–37.5 mM	[288]
	SPE/rGO-AuNPs/LDH	0.13 μM	10 μM–5 mM	[289]
	GE/DNP/LOx	15 μM	0.05–0.7 mM	[290]
	CPE-BCC-MWCNT-LOx	70 nM	0.2 μM–0.11 mM	[291]
	SPE-Glycine-LOx-GA-PEI-GCNF/PtNPs	6.9 μM	10–2000 μM	[292]
	PtE/4-aminothiophenol/SWCNT/LOx (Covalent immobilization)	4.0 μM	Up to 0.12 mM	[293]
	PtE/4-aminothiophenol/SWCNT/LOx (Adsorption)	3.0 μM	Up to 0.18 mM	
	GCE/rGO/TiO_2 NPs/LOx	0.60 μM	2 μM–0.4 mM	[294]
	SPE/PDDA-CNF-PtNPs/LOx	11 μM	25–1500 μM	[295]
	GE/ZnO NPs/LDH	4.73 nM	0.2–0.8 μM	[296]
	GE/ZnO nanowire/LOD/Nafion	12 μM	12 μM–1.2 mM	[297]
	GCE/rGO/LOx	7.5 μM	0.025–0.25 mM	[298]
	GCE/GO/LOx	5.5 μM	0.018–0.58 mM	
	PTE/TTF/CNT/LOx/Chitosan	1 mM	1–20 mM	[299]
	PET/G/LOx	0.08 μM	0.08–20 μM	[300]
	GCE/Nano-CeO_2/LDH/NADH	50 μM	0.2–2 mM	[301]
	GCE/$Pt_{30\%}$-PDDA-CMM film/LOx/Nafion	1.7 μM	5.0–50.0 μM	[302]
	GCE/VBT-VBA/LOx	3.4 μM	0.01–1.0 mM	[303]
	GCE/PDDA/LOx	10 μM	0.03–0.50 mM	
	GE/3DOM gold film/DTSP/LOx	3.93 μM	Up to 1.3 mM	[304]
	GE/3DOM gold film/LOx	16.22 μM	Up to 0.6 mM	
	Glass-AuE/ZnO nanorods/GA/LOx	0.1 μM	0.1 μM –1.0 mM	[305]
	GE/ZnO nanotetrapods/LOx/Nafion	1.2 μM	3.6 μM–0.6 mM	[306]
	GE/LOx/Alginate/PDDA	50 nM	2.0 μM–3.6 mM	[307]
	SPE/MWCNT/PS/Meldola's blue/LOD	0.37 μM	1–20 μM	[308]
	SiO_2-GE/MoO_3 nanowire/LOx/Nafion	0.15 mM	0.5–8 mM	[309]
	SPE/CoPC/Nafion/Mesoporous silica-LOD	18.3 μM	18.3 μM–1.5 mM	[310]
	GCE/Fe_3O_4/MWCNT/LDH/NAD^+	5 μM	50–500 μM	[311]
	GE/ZnO NPs-MWCNT/LOx/Nafion	4.0 nM	0.01–10 μM	[312]
			10–200 μM	
	GCE/Nitrogen-doped CNT/TBABr-Nafion	4.1 μM	14–325 μM	[313]
	GE/MPTS/AuNPs/LOx	4.0 μM	50 μM –0.25 mM	[314]
	PGE/MWCNT/ZnO NPs/PDDA	6.0 μM	0.2–2.0 mM	[315]
	GE/Nanostructured rough Au-DTSP-LOx	21.5 μM	Up to 1.2 mM	[316]
	PtE/PB/PPy-LOx from the species *Pediococcus*	-----	0.5 μM–0.5 mM	[317]
	SPE/Meldola's Blue-Reinecke salt/NAD^+/LDH	0.55 mM	0.55–10 mM	[318]
	PtE/Nafion/Albumin–mucin hydrogel/LOx/ Polycarbonate membranes	0.8 μM	2–1000 μM	[319]
	GE/pTTCA/MWCNT/LDH	1.0 μM	5–90 μM	[320]
	SPE/CoPC/LOx	289 μM	Up to 6 mM	[321]
	GE/Pt-black NPs/LOx	-----	1–20 mM	[322]
	GCE/Pt NPs/MWCNT/Sol gel-LOx	0.01 mM	0.2–2.0 mM	[323]
	GE/Nafion/$H_2Ti_3O_7$ nanotubes/LOx	0.2 mM	0.5–14 mM	[324]
	GE/CNT-PVI-Os-Chitosan-LOx	5 μM	Up to 1 mM	[325]
	PtE/Albumin–mucin hydrogel/GA/LOx/ Polycarbonate membranes	0.7 μM	Up to 1.5 mM	[326]
	GCE-MWCNT-Silica sol gel-LOx	0.8 μM	0.3–1.5 mM	[327]
	GE/AuNPs/LDH	100 nM	Up to 0.8 mM	[328]
	FET (Nano-Si_4N_3-PAA-LDH)	0.2 μM	Up to 10 μM	[329]
	CNTPE/Meldola's blue/LDH	7.5 μM	0.10–10 mM	[330]
	GCE/LOx	0.9 μM	Up to 0.2 mM	[331]

Table 6 (continued)

Metabolic biomarker	Type of affinity assay	LOD	DLR	References
	GCE/Nanoscaled CoPc/LOx/Chitosan-MnO_2 NPs	8 μM	0.020–4.0 mM	[332]
	ITO/Poly(An-co-FAn)/GA/LOx	0.1 mM	0.1–0.6 mM	[333]
L-phenylalanine	GE/GO-Chitosan/PDH	416 nM	500 nM–15 mM	[334]
	GE/$nPrNH_2$-MCM-41/PDH	0.006 μM	0.01–0.15 μM	[335]
L-proline	GCE/Chitosan-Cysteine/$nPrNH_2$-MCM-41-Fe_2O_3-Chitosan-PRODH	0.006 μM	0.01–0.15 μM	[336]
Tyrosine	GCE/rGO/Hemin	75 nM	0.5 μM–0.5 mM	[337]
	GCE/MWCNT/PAMAM/Hemin	10 nM	0.1–29 μM	[338]
	GCE/Cysteamine/AuNPs	40 nM	0.1 μM–0.3 mM	[339]
	GCE/L-serine polymer film	0.1 μM	0.3 μM–0.1 mM	[340]

GCE, Glassy carbon electrode; PDA, Polydopamine; AOx; Alcohol oxidase; BIPN, 2-(4-Nitrophenyl)-4,7-di(thiophen-2-yl)-1H-benzo[d]imidazole; FcAOx, Ferrocene entrapped alcohol oxidase; FcMe, Ferrocene methanol; HRP, Horseradish peroxidase; MPTS, (3-Mercaptopropyl)-trimethoxysilane; DNPs, Diamond nanoparticles; PSSG, Partial sulfonated (3-mercaptopropyl)-trimethoxysilane sol-gel; ADH, Alcohol dehydrogenase; PBCB, Poly brilliant cresyl blue; PPy-F127, Polypyrrole-Pluronic F127; PDDA, Poly (diallyldimethylammonium chloride); PAA, Polyacrylic acid; G, Graphene; HDT, 1,6-Hexanedithiol; GA, Glutaraldehyde; FC, Ferrocene; AA, Azure A; TO, Thioctic acid; PANI, Polyaniline; PDDA, Poly(diallyldimethylammonium); PET, Poly (ethylene terephthalate); PTH, Poly(thionine); LOx, Lactate oxidase; PB, Prussian blue; CPE, Carbon paste electrode; SPE, Screen printed electrode; CNF, Carbon nanofiber; CFE, Carbon film electrode; $Ru(bpy)_3^{2+}$, Tris(2,2'-bipyridine) ruthenium(II); PNR, Polyneutral red; CoPC, Cobalt phthalocyanine; VBT, 4-vinylbenzyl thymine; GCNF, GCNF, Graphitized carbon nanofibers; CPZ-SO, Chlorpromazine-sulfoxide; VBA, 4-Vinylbenzyl triethylammonium; PDDA, Polycation polydiallyldimethylammonium; PPY_{Ox}, Overoxidized non-conducting polypyrrole; BCC, Benzo[c]cinnoline; LDH, Lactate dehydrogenase; PyOx, Pyruvate oxidase; CMM, Carbon mesoporous material; PS, Polysulfone; PGE, Penciled graphite electrode; TBABr, Tetrabutylammonium bromide; DTSP, Dithiobis-N-succinimidyl propionate; EDP, Electrodeposition paints; PVI-Os, (Polyvinylimidazole-Os); pTTCA, Poly-5,2'-5',2”-terthiophene-3'-carboxylic acid; ($FcMe_2$-LPEI), Dimethylferrocene-modified linear poly(ethyle- nimine) hydrogel; Poly(An-co-FAn), Polyaniline-co-fluoroaniline; PRODH, Proline dehydrogenase; APTES, 3-Aminopropyl triethoxysilane; FSN, Functionalized silica nanoparticle

Conclusion

With increasing acute and chronic diseasese, sensitive and reliable diagnostic tools will improve treatment outcomes. However, the conventional diagnostics used for such purposes are extremely powerful; most of these are limited by time and cost-consuming protocols and require higher volume of test sample. In this review, we have presented a snapshot of the recent developments in the field of electrochemical biosensors and an overview of signal amplification strategies based on the nanomaterials. However, researchers have developed many signal enhancement strategies in the fabrication of electrochemical biosensors such as nuclease amplification, rolling circle amplification, catalyzed hairpin assembly amplification and etc. The nanomaterial-assisted signal amplification is more efficient because that they are not only employed as ideal carriers to immobilize various bioreceptors but also act as the sorbents for the accumulation of redox indicators. One of the fascinating aspects of nanomaterials is that the chemical properties of their surface can be manipulated by surface modification and functionalization. Furthermore, some of these nanomaterials exhibit unique electrical conductivity with high performance for electrochemical biosensors. The combination of high affinity and specificity of bioreceptors and unique properties of nanomaterias provides promising opportunities for various biosensing applications. Despite considerable progresses in this area, there are definitely challenges that must be addressed. (I) Most of electrochemical biosensors have been constructed for in vitro detection of metabolic biomarkers; therefore, the design of biosensors for in vivo measurements should be a priority in the future. The real-time measurement of metabolic biomarkers requires the development of in vivo biosensors, which necessitates the synthesis of non-toxic nanomaterials, improved stability of enzymatic immobilization and enhanced resistance to substance interference. (II) The fabrication of multiplexed nanoscale biosensors for simultaneous detection of different analytes has still remained a major challenge at the nanotechnology frontier. Development of biosensors that allow for simultaneous detection of multiple metabolic biomarkers of a disease can achieve higher detection sensitivity while reducing false positives. For this purpose, integration of analytical technologies on a single platform is recommended. (III) The design of microfluidics platforms for electrochemical biosensors is required to overcome the limitations of conventional bioassays through the development of biosensors that can provide continuous, in situ and rapid measurement of targets. The developments in microfluidics should be directed towards fabrication of biomimetic human organoid models that simulate both the biology and the physiological microenvironment of the human system, termed organs-on-chips. Microfluidic organs-on-a-chip platforms allow the continual monitoring of (multiple) secreted biomolecules in a noninvasive manner while consuming only small volumes of media. (IV) Despite all significant

achievements in the design and development of highly sensitive and selective electrochemical biosensors, there is a need to address the issue of transition from development stages towards commercialization of biosensors for point-of-care diagnostics of diseases. By driving the development of suitable bench-top technology through product development, other practical aspects including portability, costs and fabrication techniques can also be examined. These biosensors will then be well poised for speedy translation into point-of-care diagnostics. Finally, it is expected that the nanomaterials will have a great practical foundation in design of novel biosensors for point-of-care clinical diagnostics. Taking into account the continuous progress in the development of novel nanomaterials, the application of new electrochemical sensing scaffolds based on multifunctional nanomaterials is expected to be widely developed in the future.

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