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RARE METALS

REVIEW

Recent advances on bioreceptors and metal nanomaterials-based electrochemical impedance spectroscopy biosensors

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Abstract Metal-based nanomaterials have a wide range of applications in energy conversion, catalysis, bioimaging, and sensors. In our review, we mainly introduce metal nanomaterials-based electrochemical impedance spectroscopy (EIS) biosensors in medical healthcare, environmental monitoring, and food safety instructively, with collecting and analyzing the current achievement of predecessors. In general, metal nanomaterials-based EIS biosensors can be divided into four components, in which bioreceptors and metal nanomaterials transducers are vital for designs. Bioreceptors and metal nanomaterials determine the feasibility, specificity, sensitivity and simplicity of manufacturing and operations. With the demonstration and discussion of bioreceptors and metal nanomaterials of biosensors in different fields, our review aims to assist brief acknowledgement of current state-of-the-art achievement and provide our insights for the future development.

Keywords Metal nanomaterials; Electrochemical impedance spectroscopy (EIS); Biosensors; Bioreceptors

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1 Introduction

Nature is the mother of curiosity and inspiration, for which has tested and evolved the recognition among specific substance over the past billions of years, especially for modern sensor researchers. Among all the recognition, the identification between target molecules and biomolecules has a promotion for sensor designing with its diversity [1], accuracy [2], and programmability [3]. Therefore, a variety of biosensors have been synthesized to detect the presence of target molecules and cellular structures or changes of related parameters in health care monitoring [4], food safety sensing [5], and environmental protection detection [6]. However, biosensors demand new concepts to achieve low cost due to the difficulty in forming required biomolecules, low durability of the biomolecules, and time-consuming way for sensing through heavy facilities. Herein, new materials and sensing methods are introduced into biosensors for solving the mentioned challenges. For new materials, such as metal materials [7], carbon materials [8] and non-metallic/carbon materials [9] have assisted biosensors, among which metal materials have been maturely and widely used. For new sensing methods, they mainly include electrochemical [10], photoelectric [11], field-effect transistor [12], fluorescence [13], etc., in which electrochemical biosensors are one of the most popular type.

Among all candidate materials that can be applied to biosensors, metal nanomaterials stand out and play a significant role. Generally, the metal nanomaterials exhibit diverse properties, such as variety of nanostructures [14], high conductivity [15], abundant chemical active sites [16], and high surface-to-volume ratio [17], which are curtail factors for optimizing biosensors performance. Metal

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nanomaterials typically contain three classes of metal simple substance nanomaterials, metal compound nanomaterials, and alloy nanomaterials, which differs in properties from each other, but the alternativity of properties offers great potential for adapting to different sensing requirements. However, most of the chosen metal nanomaterials are based on precious metal, which is the barrier to outpatient and commercialization. Thus, the upcoming discussions include various biosensors based on non-precious metal nanomaterials.

There are numerous electrochemical sensing methods, among which electrochemical impedance spectroscopy (EIS) is indispensable for evaluation, because it is a sensitive approach to detect the occurrence and change of electrochemical events that appear on the electrode/electrolyte interfaces. Nearly 120 years have passed since Oliver Heaviside first described EIS in the late nineteenth century [18]. In EIS theory, electrochemical events cause current to flow at the electrode–electrolyte interfaces and change the electrical characteristics of the interfaces. The current transmitted to the external circuit through the interface contains a Faradaic component and a non-Faradaic component. The Faradaic component results from the directional movement of redox electrons, while the electrons in charging and discharging double-layer capacitors result in the inevitable non-Faradaic component [19]. These two types of components response to corresponding signals of current (voltage) under stimulations of small amplitudes, different frequencies, and alternating sinusoidal voltage (current) signals. These corresponding signals can be transformed to impedance or admittance in the equivalent circuits to help us analyze electrochemical events caused by the above identifications. Specifically, the biological identifications can be divided into three types which cause electrochemical events. (a) Bio-Faradaic current. The bio-Faradaic current will appear on the electrode when targets bind to their bioreceptors and the corresponding redox reaction occurs. This electrochemical event can be captured by EIS. (b) Steric hindrance. The difficulty of redox non-target molecules that exist in the electrolyte solution, on bioreceptor to diffuse or attract to the electrode surface changes, due to the binding of the target to its bioreceptor and the coming size change. It results in a certain steric hindrance change. Through EIS theory, steric hindrance change will manifest itself as a change in impedance. (c) Charge hindrance. The difficulty of redox non-target molecules that remain in the electrolyte solution or on bioreceptors to diffuse or attract to the electrode surface changes, due to the binding of the target to its bioreceptor and the charge change resulting from the charge carried by target. This causes a certain charge hindrance change. Charge hindrance change will manifest as impedance change as well. Furthermore, steric hindrance and charge hindrance usually occur simultaneously. Therefore, it has shown great usability in multiple biosensors [20–22].

Herein, it is crucial and instructive to collect and analyze the current achievement of predecessors. In general, metal nanomaterials-based EIS biosensors can be categorized into 4 components, as shown in Fig. 1, which are targets, bioreceptors, metal nanomaterials transducers and outputs. It is a top-down linear logic chain from the target to the output where the bioreceptors and metal nanomaterials transducers are vital for designs. Although targets limit the selection of bioreceptor, the adaptation between bioreceptors and metal nanomaterials transducers determines the feasibility, specificity, and sensitivity for metal nanomaterials-based EIS biosensors. Moreover, some metal nanomaterials transducers can also function as bioreceptors because of their potential catalytic ability to switch on the recognition under a set environment. With the demonstration and discussion of bioreceptors and metal nanomaterials transducers for biosensors in different fields, our review aims to assist brief cognition of current achievement and inspire tremendous innovation in the future.

2 Different bioreceptors

2.1 Nucleotide bioreceptors

2.1.1 Nucleic acids

Nucleic acids are indispensable materials for all known creatures. Due to their different compositions, they can be divided into deoxyribonucleic acid (DNA) and ribonucleic

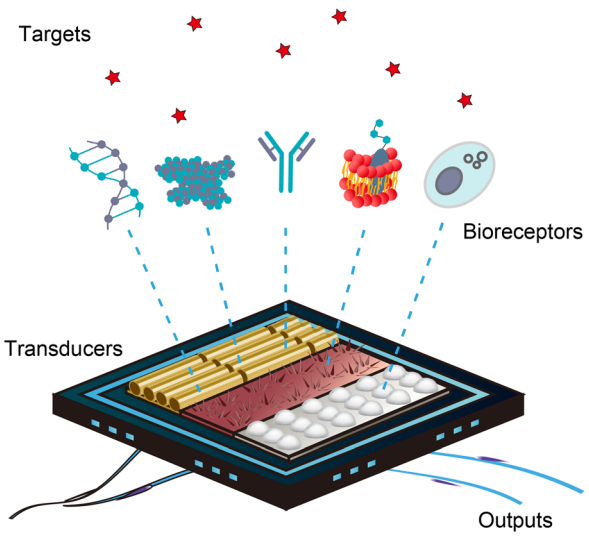

Fig. 1 Structure of metal nanomaterials-based EIS biosensors

acid (RNA). DNAs and RNAs are the fundamental materials for heredity, variation, transferring, and expression of bioactivities for organism. The linear arrangement of deoxyribonucleotides and ribonucleotides leads to their abundance and encodability [23]. In the meantime, the covalent bond between them and the simple linear structure bring DNAs and RNAs much higher stability than common proteins. Moreover, every deoxyribonucleotide and ribonucleotide has a nitrogen-containing base that can be paired with each other particularly, which cause their unique specific recognition. For example, steric hindrance change occurs after prostate specific antigen (PSA) attaching to the combine of single-stranded deoxyribonucleic acid (ssDNAs) and aptamers (Fig. 2a). Meanwhile, the negative charge of the PSA leads to charge steric hindrance. These two types of hindrance affect impedance and generate special signal for EIS detection. Therefore, nucleic acid-based EIS biosensors are very sensitive and widely developed. Xu et al. [24] developed a DNA biosensor for the sensing of *Escherichia coli* (*E. coil*) O157:H7 with a broader range (1.0×10^{-14}–1.0×10^{-8} mol·L^{-1}) and a more sensitive limitation (3.584×10^{-15} mol·L^{-1}). Cai et al. [25] proclaimed biosensors for Hg^{2+} detecting based on DNA hydrogel, showing the limitation down to 0.042 pmol·L^{-1}, with sensitivity and selectivity between 0.1 pmol·L^{-1} and 10 nmol·L^{-1}. Chen et al. [26] introduced a DNA biosensor for the detection of hepatitis B virus DNA with R^2 values of 0.801 in the linear range of 10^2–10^3 and R^2 values of 0.996 in the linear range of 10^3–$10^{5.1}$, respectively.

2.1.2 Aptamers

Aptamers, on the contrary, are single-stranded nucleic acids which are obtained by systematic evolution of ligands by exponential enrichment (SELEX) mostly. Due to their bare nitrogen-containing bases and the linear arrangement of nucleic acid, aptamers show the availability of modification, the abundance of functionalization and the controllability of secondary structures [27]. With these properties, aptamers are compatible for specific biorecognitions, which is similar to the selective biorecognitions of proteins, relying on the unique 3D structures matching variety of targets, such as nucleic acids and proteins (Fig. 2b) [28]. Besides, aptamers can be designed as non-fixed bioreceptors for the targets, which upgrades the biorecognitions from a surface to the whole solution, thus greatly increasing the occurrence probability of biorecognitions and leaving the biosensor with lower detection limitation. Tan et al. [29] invented an aptamer biosensor for the detecting of Hg^{2+} in water environment with a sensitivity down to 0.5 nmol·L^{-1}. Ensafi et al. [30] claimed a biosensor based on aptamer-Au modified graphite for the existence of insulin, which showed the linear range of 1.0–1000.0 nmol·L^{-1} and a limit of 0.27 nmol·L^{-1}. Istamboulié et al. [31] reported an aptasensor for the existence of aflatoxin M1 in dairy products after 0.2 μm poly tetra fluoroethylene (PTFE) filtration, whose concentrations vary from 20 to 1000 ng·kg^{-1}.

2.1.3 Molecular beacons

Molecular beacons (MBs) are single-chain nucleic acids designed as a shape of hairpins, which are first reported in 1996 [32]. Similar to aptamers, their distinctive structures show tremendous possibilities of biosensing detection. The nitrogen-containing bases from the single chains help researchers to shape them into potential variable structures. When the target molecules, including DNAs and RNAs, are combined with MBs, the hairpin-shape MBs will forcibly expand to form a linear structure due to the complementary base pairing, as shown in Fig. 2c [33]. In contrast, some other molecules, such as proteins and peptides, show the ability of folding MBs into hairpin-like shape. Through the above-mentioned biomolecular transformation, electrochemical event labels (EELs) will lengthen or shorten the distance to the electrode surface, functionalize at the 3′-end and 5′-end of MBs, change the distance of electron tunneling and further affect the electrical signal. In electrochemical biosensing, methylene blue (MTB) [34] and ferrocene (Fc) [35] are widely used as EELs, but metal particles [36] and metal organic framework (MOF) [37] are tagged more these days because of the difficulty of preparation of MTB- or Fc-based EELs. Li et al. [38] invented a biosensor with molecular beacon combining with nafion-graphene composite film modified screen-printed carbon electrodes (nafion-graphene/SPCE) for the sensitive existence of human immunodeficiency virus-1 (HIV-1) in homogeneous solutions, which showed a linear range from 40 nmol·L^{-1} to 2.56 μmol·L^{-1} and a determination limit of 5 nmol·L^{-1} (signal-to-noise ratio $S/N = 3$). He et al. [39] reported a biosensor for nicotinamide adenine dinucleotide (NAD^+) detecting with the help of MB-like DNA and *E. coil* DNA ligase, which had a linear response from 3 nmol·L^{-1} to 5 μmol·L^{-1} and a determination limit of 1.8 nmol·L^{-1}. Xiong et al. [40] announced a reusable molecular beacon biosensor with accessibility for the sensitive sensing of mercury ions (Hg^{2+}) with a liner range from 0.5 to 5000 nmol·L^{-1} and a determination limit of 0.08 nmol·L^{-1}.

2.2 Protein bioreceptors

2.2.1 Enzymes

Enzymes are protein molecules that reduce the activation energy of biological reactions to increase the rates of

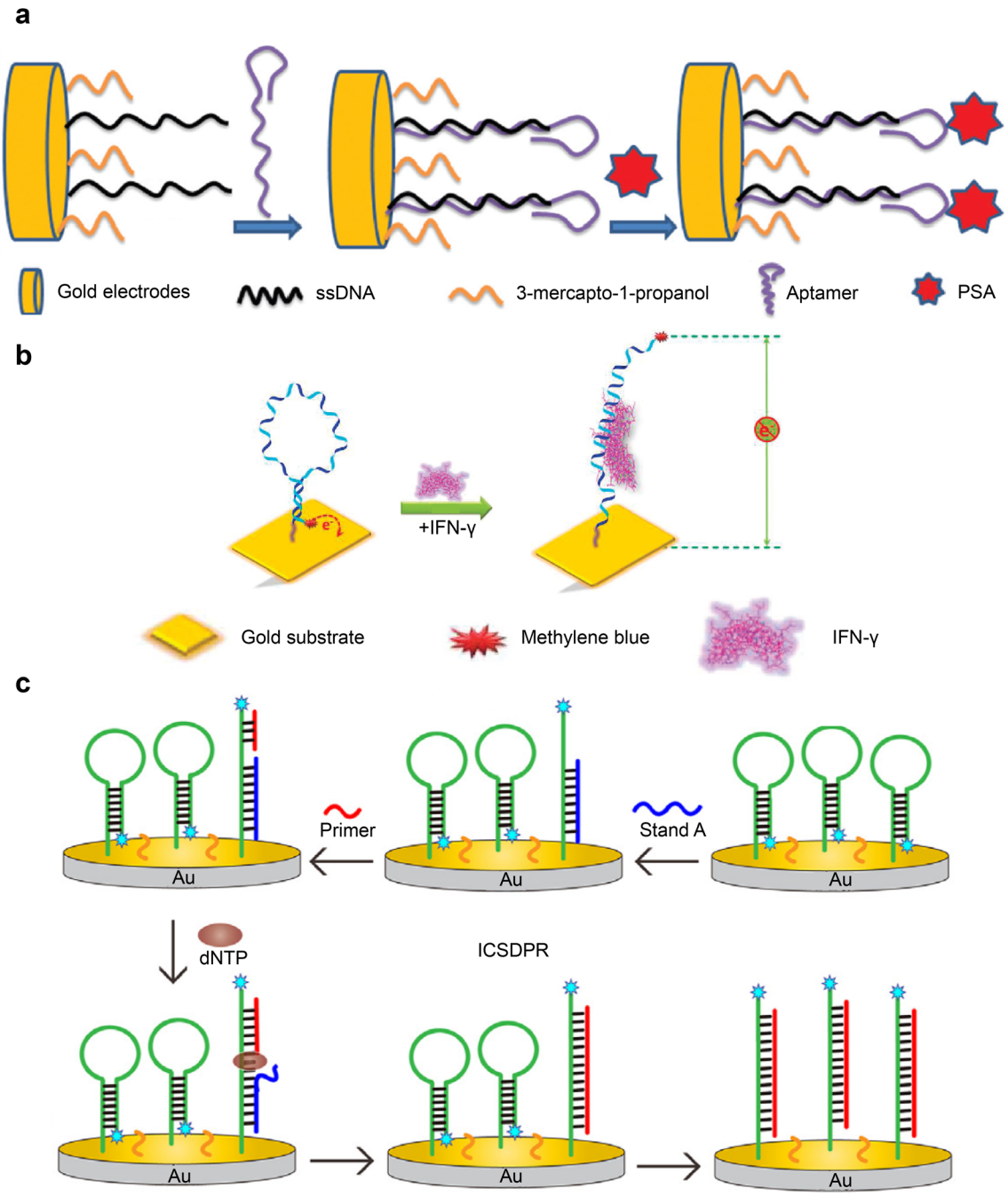

Fig. 2 Structure of nucleotide bioreceptors. **a** Linear arrangement of nucleic acids. Reproduced with permission from Ref. [23]. Copyright 2015, Royal Society of Chemistry. **b** Hair-pin structure change of aptamers, where IFN-γ is interferon. Reproduced with permission from Ref. [28]. Copyright 2010, American Chemical Society. **c** Structure change of MBs, where dNTP is deoxynucleotides and ICSDPR is isothermal circular strand displacement polymerization reaction. Reproduced with permission from Ref. [33]. Copyright 2021, Elsevier B.V

reactions. Through their unique 3D structures and abundant secondary frameworks, enzymes provide specific binding sites for substrates of biological reactions (Fig. 3a) [41]. When enzymes accelerate biological reaction, electrochemical events occur at the interface, which generate redox electron movement, cause bio-Faradic current, and change the interface electrical characteristics. Therefore, researchers have invented variety of enzyme receptor biosensors by direct enzymatic methods and enzyme-linked methods to detect enzyme targets around the electrode/electrolyte interfaces. Bouyahia et al. [42] reported a bovine liver catalase biosensor to detect catalase reaction

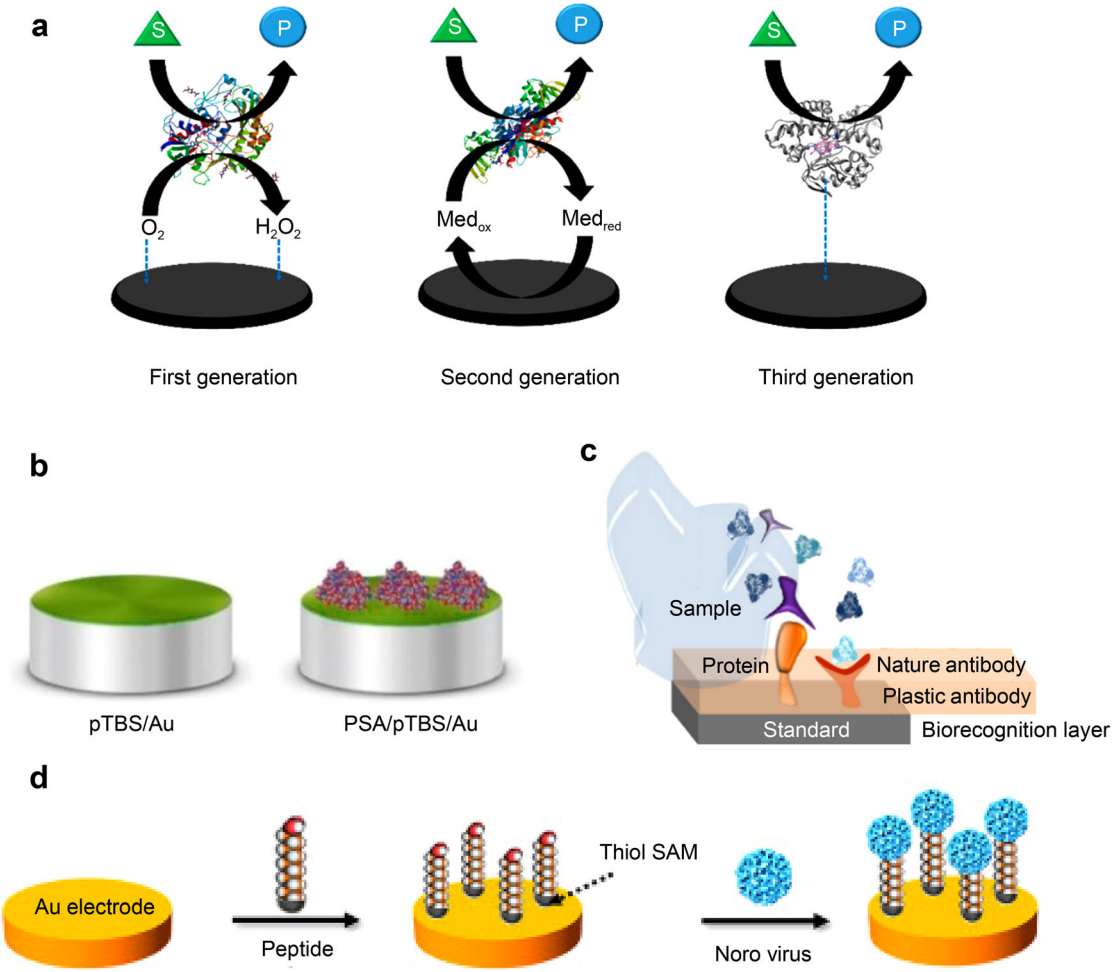

Fig. 3 Protein bioreceptors. **a** 3D structures and abundant secondary frameworks of enzymes, where S is receptor substrate, P is product, Med_{ox} is oxidation mediators, and Med_{red} is reduction mediators. Reproduced with permission from Ref. [41]. Copyright 2019, MDPI. **b** Demonstration of receptor-based biosensors, where pTBS is electrically-conducting poly[toluidine blue]. Reproduced with permission from Ref. [45]. Copyright 2020, Elsevier B.V. **c** Example of receptor-based biosensors. Reproduced with permission from Ref. [51]. Copyright 2018, Elsevier B.V. **d** Structures of a peptide-based biosensor, where SAM is self-assembly monolayer. Reproduced with permission from Ref. [58]. Copyright 2018, Elsevier B.V

with cyanide as ligand and inhibitor. Mayorga et al. [43] announced a real-time biosensor relied on glucose oxidase that responds linearly to glucose consistence from 0 to 20 $mmol \cdot L^{-1}$. Sundararam et al. [44] invented a urease biosensor whose maximum velocity (V_{max}) was 5000 $\Omega \cdot min^{-1}$. Even though enzymes can achieve precise identification according to the three mentioned quotes, their vulnerability and high production costs still restrict their wide applications.

2.2.2 Receptors

Receptors, different from enzymes, are protein molecules which recognize signal ligand molecules from inside or outside of cells to adjust cell functions, showing in Fig. 3b [45]. They are highly evolved to detect their target signal molecules with outstanding specificity and sensitivity. Receptors can be divided into three types based on their different functions: relay, amplify, or integrate a signal [46]. These three functions lead receptors compatible for more electrochemical events in biorecognition. Specifically, neurotransmitters or other intercellular secretions cause ion channels on the surface of the cell membrane to open or close, which in turn trigger membrane electrical signals. Although this current signal is not self-generated bio-Faradic current by targets, the behavior of membrane protein is also caused by the redox function of adenosine triphosphate (ATP). In addition, these functions have great prospects in programming logic circuits to form biochips. Khadka et al. [47] reported a fruit fly receptor biosensor to detect odorant molecules down to femtomolar concentrations. Doornbos et al. [48] invented a $mGlu_2$ receptor biosensor to research its pharmacology, as the $mGlu_2$ receptor is a medicine target for many psychiatric disease

treatments. Mayall et al. [49] announced a lipopolysaccharide biosensor using TLR-4 protein dimers to detect Gram-negative bacteria with a high sensitivity and insensitive to both Gram-positive bacteria and virus. However, due to the hydrophilic and hydrophobic properties of the cell membrane phospholipid bilayer, there are certain obstacles to the purification and expression of the receptor protein [50].

2.2.3 Immunoreceptors

Immune systems are the fundamental systems for animals to protect them from various microbial infections or cellular carcinogenesis. Immune systems can be divided into two categories, nonspecific immune and specific immune. Between them, specific immunity has huge biosensor potential due to its unique antigen–antibody response. Antigens are the specific molecules that are different from autologous tissue cells and mostly greater than 10,000 in relative molecular mass. Antigens trigger the generation of antibodies in specific immune response, which is humoral immunity produced by immune B cells. Antibodies produced in this way have specific recognition functions for various antigens. The specific bonding between antigens and antibodies is shown in Fig. 3c [51]. This combination results in an increase in the size of the molecules anchored on the electrode surface and a change in the surface charge of the electrode due to the chargeability of the target molecule. This directly leads to changes in steric hindrance and charge hindrance, which are then captured by EIS as characteristic signals, leading to the invention of many biosensors with antibody receptors. Tubía et al. [52] reported an antibody-based interdigitated biosensor to monitor brettanomyces in wine and cider spoilage filed, which showed approximately 55% higher sensitivity values in low-frequency area than its competitors. Nidzworski et al. [53] announced an antibody biosensor with boron-doped diamond electrodes, which reached a limitation of 1 $fg{\cdot}ml^{-1}$ in saliva buffer for the M1 protein of influenza virus. Jacobs et al. [54] invented an antibody nanochannel biosensor to detect the erythromycin in different water environment and achieved a sensitivity of 0.001 parts per trillion. Besides, different specific antibody components still show non-negligible potential for biosensors, such as antibody fragments [55], single-chain variable fragments [56], and monobodies [57].

2.2.4 Peptides

Peptides, similar to the relationship between nucleic acids and aptamers/molecular beacons, are the precursor molecules of tremendous number of proteins, which are designed in linear or cyclic chain shapes, as shown in Fig. 3d [58]. Differing from the frangibility and costliness of proteins, peptides can be acquired easily by chemical synthesis methods in laboratories or in factories, while most proteins require participation of eukaryotic cell engineering. Analogous to the editable sequence of nucleic acids, peptides perform an exceeding variability due to their twenty-two kinds of amino acid base elements, while nucleic acids are base from eight kinds of riboses with smaller numbers of nucleic acid analogues used widely including peptide nucleic acid (PNA), morpholino (MNA) and threose nucleic acid (TNA). For example, the linear peptide chains are anchored to the surface of the gold electrode via Thiol SAM, as shown in Fig. 3d. The peptide chain captures the Noro virus, the overall volume increases, so that the protein shell of the Noro virus has a certain charge. This changes the steric hindrance and charge hindrance on the electrode surface, which in turn induces the change of the EIS signal. Accordingly, peptides reveal tremendous potential of combining positions with diverse bonding methods without complex secondary structures. Cho et al. [59] proclaimed a novel affinity peptide-incorporated biosensor for the detection of neutrophil gelatinase-associated lipocalin (NGAL) under acute kidney injury and diabetes with a more sensitive limit of detection (LOD) of 1.74 $ng{\cdot}ml^{-1}$ compared to a SWV's LOD of 3.93 $ng{\cdot}ml^{-1}$. Furthermore, the peptide they introduced was designed with the information of the M13 phage display library, which shows an alternative way for peptide biosensors. Malvano et al. [60] obtained a nisin-based EIS biosensor using its antimicrobial properties and responding the distinct impedimetric behaviors captured after the exposure to pathogenic and non-pathogenic *Salmonella strains* separately, with a limit of 1.5×10^1 colony-forming units (CFU)$\cdot ml^{-1}$. Shi et al. [61] developed a label-free biosensor with affinity peptides selected from phage-displayed peptide library and modified later, which was equipped with a low sensing limit of 20 $CFU{\cdot}ml^{-1}$ and a liner scope from 2×10^2 to 2×10^6 $CFU{\cdot}ml^{-1}$.

2.3 Glycan and lipid bioreceptors

Glycans, also called as polysaccharide, mix monosaccharide with proteins and lipids, which are one of the main biomolecules. They play a crucial role in the biorecognition between cell–cell, pheromones and immune molecules, obtaining far more information and ultra-higher structural variability compared to nucleic acids, proteins or peptides [62]. Recently, glycemics has been developed rapidly and brought a new and tremendous motivation for biosensors.

2.3.1 Glycoproteins and glycolipids

According to the current study, glycans are capable to be distinguished as glycoproteins and glycolipids.

Specifically, O-glycans combined through −OH of Ser or Thr and N-glycans through $-NH_2$ of a peptide sequence -Asn-X-Ser/Thr constitute glycoproteins, which is shown in Fig. 4a [63]. Besides, glycolipids contain rhamnolipids, trehalolipids, mannosylerythritol-lipids, cellbiolipids and sophorolipids, 5 derivatives in total, as shown in Fig. 4b [64]. Notably, lectin has been selected by researchers as a natural library for biosensor designing and assembling, and their interaction is concluded in Fig. 4c [65]. Glycoproteins and glycolipids, as specifically recognized cell membrane molecules, can specifically bind to target molecules. This binding leads to a significant increase in the size of bioreceptors on the biosensor surface, and the potential charge of the targets may also cause the bioreceptor to change its electrochemical properties. Then, the electrochemical events brought about by steric hindrance and charge hindrance are keenly detected by EIS for researchers to analyze the corresponding biological events. Klukova et al. [66] first announced a label-free lectin/graphene oxide (GO) biosensor without any synergy of polymer for the detection of 1 aM glycoproteins, which also revealed that GO benefited the sensitivity. Simão et al. [67] achieved a biosensor which is based on cysteine (Cys), zinc oxide nanoparticles (ZnONp), and Concanavalin A (ConA) lectin aiming to differentiate arboviruses infections, including Dengue type 2 (DENV2), Zika (ZIKV), Chikungunya (CHIKV), and Yellow fever (YFV), showing significant distinct in impedance responses. Rangel and Silva [68] proclaimed a biosensors using the lectin from Arachis hypogaea (peanut agglutinin, PNA), which showed a 7.2% increase in impedance at 100 ng of target, with very high stability under interfering proteins. Ramkumar et al. [69] introduced a biosensor for detection of dopamine by gold electrodes with thiourea linked glycolipid to synthesize polyaniline (PANI) spheres, which performed a linear scope of $\sim$ 1 to 640 $\mu mol \cdot L^{-1}$, a sensitivity range of 370 $\mu A \cdot cm^{-2} \cdot \mu mol \cdot L^{-1}$, a limit of 10 $nmol \cdot L^{-1}$, a response time of $\sim$ 5 s and a selectivity for real sample analysis.

2.3.2 Liposomes and lipid bilayers

Recently, liposomes and lipid bilayers biosensors have attracted quite a few attentions. Lipids, due to their structure in one end is hydrophilic and the other end is hydrophobic, perform excellent capability for diversity of biorecognitions. Generally speaking, liposomes are typically 20 nm–10 μm in size, while the lipid biolayers are 4–5 nm thick. This structure characteristic brings them a relatively big surface and abundant combining position, which can also designed as arrays. Overall, the hydrophilic orientation of liposomes and lipid bilayers contributes to their insulating properties. Their specific topography on the electrode surface is used to capture the specific binding targets. The electrochemical events brought about by their biorecognition are mainly changes in steric hindrance, which can be clearly detected by EIS. Thus it offers significant potential for use in biosensors, showing in Fig. 4d [70]. Khadka et al. [71] announced that OrX/Orco liposomes bind N-hydroxysuccinimide/1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (NHS/EDC)-activated self-assembled monolayers (SAMs) of 6-mercaptohexanoic acid (6-MHA) and were immobilized on gold surfaces for receptor function with the integrity of membrane, enabling their target ligands down to sub-femtomolar levels via EIS with sensitive and selective detection. Karutha and Venkataraman [72] announced a biosensor based on the vesicle structure formed by binary liposome mixture of cationic liposome N-[1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethylammonium propane (DOTAP) and the zwitterionic liposome 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) for detection of label-free DNA and streptavidin, which accessed the limit of 1×10^{-14} $mol \cdot L^{-1}$, 1 $ng \cdot ml^{-1}$ and linearity range of 1×10^{-13} to 1×10^{-13} $mol \cdot L^{-1}$, 100 ng to 1 μg, respectively. Gomes et al. [73] constructed a biosensor relied on nitric oxide reductase constructed with phospholipid bilayer and carbon nanotubes, which exhibited a sensitive Michaelis–Menten constant (4.3 $\mu mol \cdot L^{-1}$), broad linear range (0.44–9.09 $\mu mol \cdot L^{-1}$), precise limit (0.13 $\mu mol \cdot L^{-1}$), promising repeatability (4.1% RSD), reproducibility (7.0% RSD), and stability (ca. 5 weeks).

2.4 Glycan and lipid bioreceptors

Cells, standing on a more integral and macroscopic level than molecules mentioned above, are the fundamental elements for nearly all kinds of bioreactions. Cells provide a natural and complete environment for multiple kinds of bioreactions and accordingly show a better accuracy and more possibilities for potential subsequent bioreactions of biosensors targets. Under different target stimulants, cells preform quantizable changes, such as metabolic custom change, fluorescence, electron transmission, acquisition or release of chemicals, lysis or remodeling of biofilm and cell apoptosis, some of which can be transformed into electrochemical signals and measured (Fig. 5) [74]. Besides, cell biosensors are capable for multitargets and those bioreactions whose mechanism have not been well studied. In general, cell-based biosensors can be divided into two categories, one is fixed cell array biosensors, and the other is floated cell biosensors [74]. Fixed cell array biosensors are designed with a certain cell subsequence to detect the bio-electrochemical transforming of cells induced by targets. Floated cell biosensors are based on the 'fishing net effect' to capture cell before and after irritations. Either of these two species of cell biosensors is

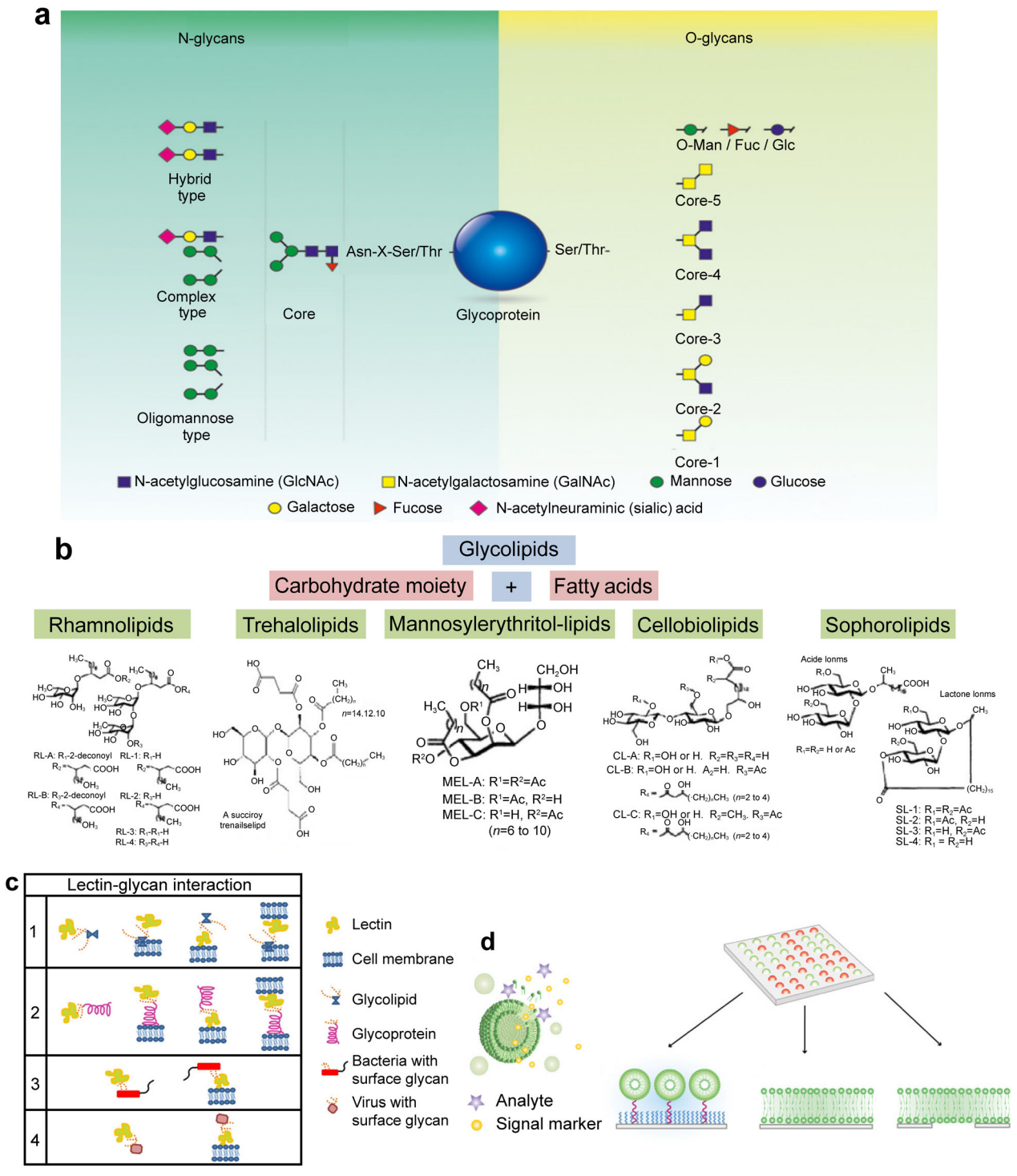

Fig. 4 Glycan and lipid bioreceptors. **a** Glycoproteins and glycolipids. Reproduced with permission from Ref. [63]. Copyright 2016, Portland Press LTD. **b** Different types and their structures of glycolipids. Reproduced with permission from Ref. [64]. Copyright 2017, Springer Science Business Media, LLC. **c** Lectin–carbohydrate interactions. Reproduced with permission from Ref. [65]. Copyright 2019, Elsevier Inc. **d** Liposomes and lipid bilayers in biosensors. Reproduced with permission from Ref. [70]. Copyright 2017, Elsevier B.V

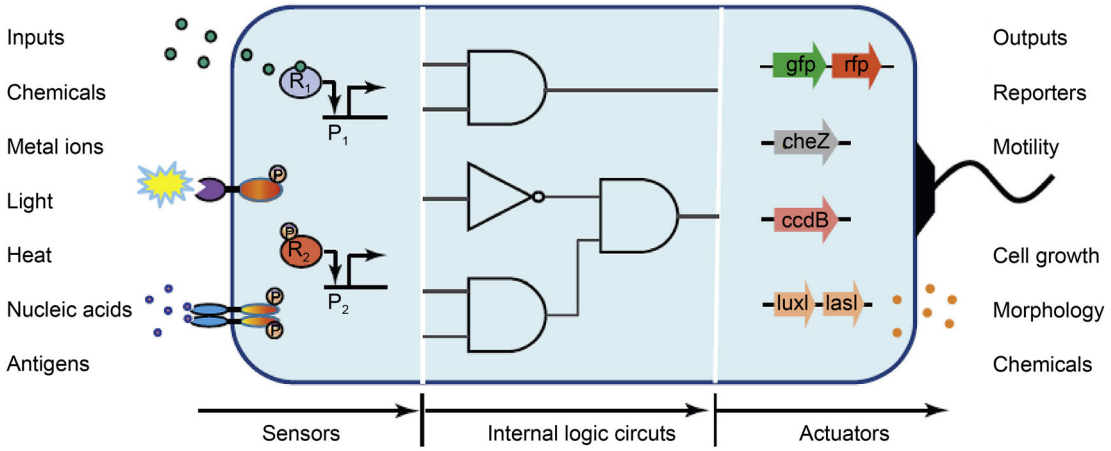

Fig. 5 General design of cell-based biosensors. Reproduced with permission from Ref. [74]. Copyright, 2019 Elsevier B.V

constructed from the multimolecular biorecognitions between cell membranes and functionalized materials, thanks to the achievements of material science and molecular biology.

With the intriguing future of cell-based biosensors, massive efforts have been contributed into this field. Classified by the type of cell used in cell sensors, they can be distinguished into prokaryote and eukaryotes biosensor. Prokaryotes are widely used in environmental monitoring and food-toxin detections for their low cultivation cost under massive usages and robust durability under external environment change. In addition, the primitive restriction of their genetic materials brings promising prospective for researchers to design and express requirements. However, because of their primitivity, biomolecules on cell membranes are relatively simple, thus limiting the diversity of biometric recognitions between nanomaterials and cells. Being distinct from prokaryotes, eukaryotes are used as bioreceptors for drug screening and disease surveillance for their larger number and better-evolved biomolecules on the membranes. Ye et al. [75] introduced a method to appraise the antioxidant effect of Ph through 3D cell modification upon a glassy carbon electrode (GCE), who had a LOD of 1.96 $\mu mol \cdot L^{-1}$ and an obvious correlation between reactive oxygen species (ROS) and impedance value (R_{et}), while the value of Ph is varying. Xia et al. [76] invented a cell biosensor for assessing the individual and mixed toxicity of deoxynivalenol (DON), zearalenone (ZEN), and aflatoxin B1 (AFB1) on Hep G2 cells, which achieved 48.5, 59.0 and 3.1 $\mu g \cdot ml^{-1}$ of half maximal inhibitory concentration (IC_{50}), respectively. Ge et al. [77] proclaimed a cell-based biosensor used to accomplish the antioxidant capacity of cell-free extracts from *Lactobacillus plantarum strains* isolated from Chinese dry-cured ham, which relies on the existence of cellular ROS (the flux of H_2O_2 released from RAW 264.7 macrophage cells) to indirectly detect changes in intracellular oxidative stress influenced by *L. plantarum strains*, with the limitation of 0.02 $\mu mol \cdot L^{-1}$ and a linear response from 0.05 to 0.85 $\mu mol \cdot L^{-1}$.

3 Metal nanomaterials-based transducers

In the previous section we focused on the different bioreceptors. In fact, in order to improve the accuracy and selectivity of the biosensor, the material and structural design of the transducers is particularly important. Numerous materials have been demonstrated their promisingly biosensing capabilities, including metal nanoparticles [78], metal compounds [79], and a variety of nanocarbon materials (constructed quantum dots [80], carbon nanotubes [81], graphene [82], and metal organic frameworks [83]), etc. In particular, the wide application of metal nanomaterials in the field of electrochemistry has greatly stimulated innovations in EIS biosensing, where they are used as biological receptors and transducers. In this section, we present various biosensors based on metal nanomaterial transducers (Table 1 [29, 55, 84–94]) which can not only combine with biological receptors to form more sensitive transducers, but their own selectivity and notable catalytic capabilities are also beneficial to inspire the development of unique biosensors.

3.1 Metal simple substance nanomaterials transducers

Gold (Au), as a typical precious metal, has been widely assembled in EIS biosensing over the past serval decades. Venditti [95] published a comprehensive review and distinguished Au simple substance nanomaterials into six categories, namely spheres, robs, stars, cubes, hollow

Table 1 Summary of metal nanomaterials-based transducers

Target	Transducers composition	Detection limit	Refs.
4-nitroquinoline N-oxide	Screen-printed carbon electrode/Fe_2N NPs/reduced graphene oxide	9.24 nmol·L^{-1}	[29]
3-phenoxybenzoic acid	Glass carbon electrode/Cu-doped MoS_2 thin films	3.8×10^{-6} mol·L^{-1}	[55]
E. coli O157:H7	Gold electrodes/1,6-hexadithiol/AuNPs	48 CFU·ml^{-1}	[84]
Glycerol	Gold electrode/molecular imprinted polymer/acrylamide/bisacrylamide/AuNPs	0.001 μg·ml^{-1}	[85]
DNA	Pt electrodes/polyaniline nanowires/AgNPs	2.80×10^{-15} mol·L^{-1}	[86]
H_2O_2	Screen-printed carbon electrode/PtNPs	24.9 nmol·L^{-1}	[87]
Glucose	Cu electrode/monolayer and bilayer graphene/CuNPs	1.39 μmol·L^{-1}	[88]
Acetylcholine	Glass carbon electrode/acetylcholinesterase/Fe_2O_3 nanoparticles/poly (neutral red) film	1.04 μmol·L^{-1}	[89]
H_2O_2	Glass carbon electrode/MnO_2/graphene nanosheets	0.19 μmol·L^{-1}	[90]
Aeromonas hydrophila	Glass carbon electrode/ZnS_2 nanospheres	1×10^{-13} mol·L^{-1}	[91]
Bisphenol A	Carbon paste electrode/TiN/reduced graphene oxide	0.19 nmol·L^{-1}	[92]
Glucose	Screen-printed carbon electrode/hierarchical Au-Ni alloy/conductive polymer	0.29 μmol·L^{-1}	[93]
Organophosphate pesticides	Glass carbon electrode/Pd–Ni nanowires/monolayer MoS_2 nanosheet	0.05 pmol·L^{-1}	[94]

particles and capsules/cages, as shown in Fig. 6. Among all these shape types of Au simple substance nanomaterials, spherical particles are most frequently used in EIS biosensing. Au spherical particles are a potential material for transducer with several properties leading to its selection: (1) high specific surface area, (2) high conductivity, (3) non-toxicity and (4) abundant bonding forms. As is well known, nanoparticles have high specific surface area. More importantly, gold has high conductivity, with a theoretical conductivity of 4.25×10^7 S·m^{-1}, quite close to 6.30×10^7 S·m^{-1} for silver and 5.96×10^7 S·m^{-1} for copper, which enhances the sensitivity and intensity of the electric signals coming from biorecognitions. Regarding the toxicity of Au nanoparticles, there is no uniformity, because their toxicity is caused by different sizes and surface chemical states. Several reports revealed an interesting fact that particles of around 4–5 nm are usually not toxic under acute exposure [96–98]. On the contrary, nanoparticles larger than 5 nm perform totally the opposite under the same situation resulting from high density and specific cell bioreactions [99–102]. As for the bonding forms, they can be differed into two factors: (a) covalent bonding and (b) non-covalent bonding. In general, Au−S−R and Au−NH_2−R bonds are two common covalent bonds because of the convenient functionalization with sulfhydryl groups (−SH) and amino groups (−NH_2) and the robust stabilities of these two types of bonds [103]. This effect of functionalization results from three factors: (1) the dosage of functionalized molecules, (2) the size of Au nanoparticles (AuNPs) and (3) the steric hindrance of functionalized molecules [104]. Besides, this binding occurs not only between AuNPs and biomolecules, but also between AuNPs and electrodes. Non-covalent bonds, more often designed to be emerged between AuNPs and electrodes, can be concluded as follows: direct mixing [105], electrodeposition [106] and electrostatic attraction [107]. Direct mixing contains spin coating, drip coating and stirring, using the van der Waals forces and high surface-to-volume ratio for the assembly. Electrodeposition relies on the interface redox reaction between $HAuCl_4$ and the electrode, or the self-charging properties of AuNPs by external voltage/current method to produce electric field force deposition. Notably, AuNPs always carry a negative charge, so they can achieve self-assemblage by electrostatic attraction.

With all the properties mentioned above, tremendous number of EIS biosensors based on Au simple substance nanomaterial have been invented and development these years. Khater et al. [108] announced a biosensor for the DNA detection of citrus tristeza virus, where they electrodeposited AuNPs on the electrode through the reduction of $HAuCl_4$ and attached AuNPs to hybridized target DNAs for detection with sulfate-functionalized probe DNA, using impedance as a means of evaluation, whose impedance had a linear range for consistence from 0.1 to 10 μmol·L^{-1} of synthetic DNA. Lin et al. [84] used 1,6-hexadithiol as a bridging molecule connecting gold electrodes and AuNPs to obtain an EIS biosensor for sensing *E. coli* O157:H7, with a limit of 48 CFU·ml^{-1}, three times lower than that of panel biosensors, and a broader dynamic range (up to 10^7 CFU·ml^{-1}). Motia et al. [85] invented a molecular imprinted polymer (MIP)/acrylamide/bisacrylamide

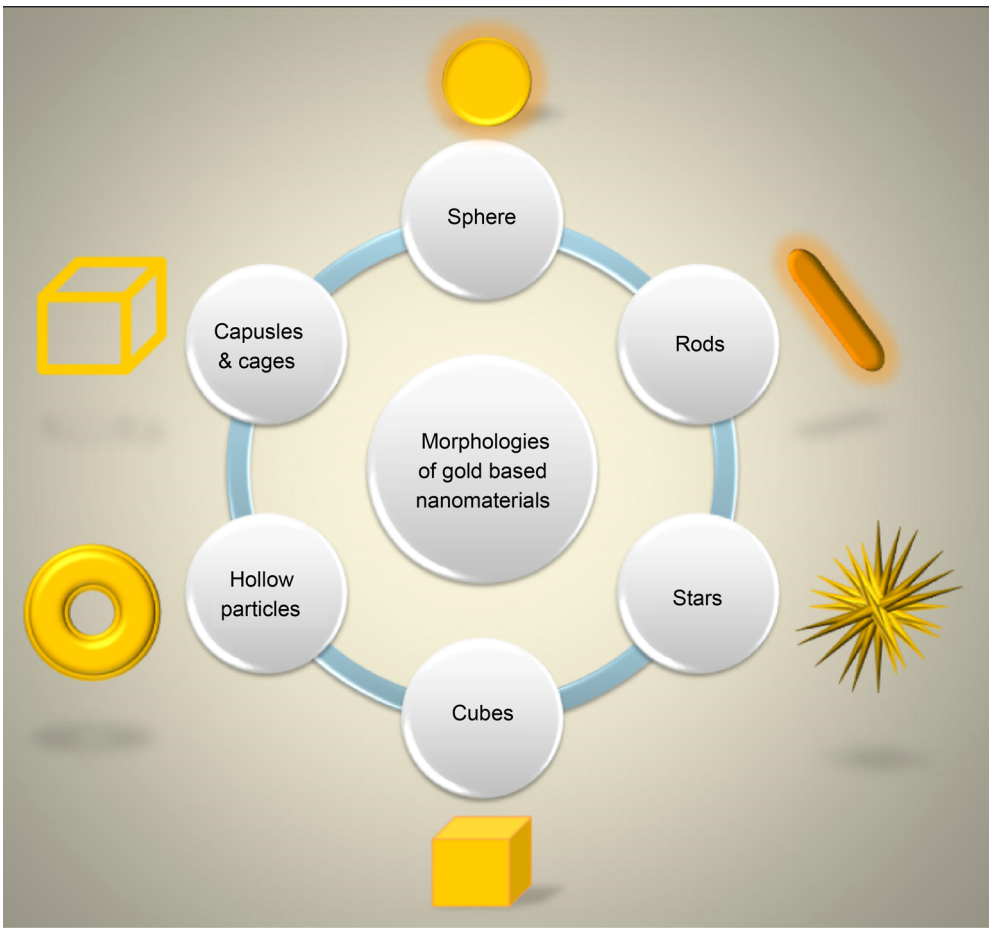

Fig. 6 Schematic representation of main morphologies of gold-based nanomaterials. Reproduced with permission from Ref. [95]. Copyright 2019, MDPI

(AAM/NNMBA) and AuNPs biosensor formed on screen-printed gold electrode (Au-SPE) for the sensing of glycerol in cosmetics, whose linear range was 20.00–227.81 $\mu g \cdot ml^{-1}$ and a determination limit of 0.001 $\mu g \cdot ml^{-1}$ ($S/N = 3$). The reason for the unique deposition of MIP to create cavities over a large area was not mentioned in their report, it might be owing to the electron withdrawal conjugation between carbon–carbon double bonds and carbonyl groups, resulting in the deposition and attachment of MIPs to AuNPs.

Since Au attracts plenty of attention in this field, silver (Ag), as a family member of Au, also plays an essential role as transducers. Douaki et al. [109] reported a biosensor based on the Ag−S binding between 1,8-octanedithio and silver nanoparticles (AgNPs), showing that the covalent linkage of sulfhydryl groups was also applicable to AgNPs. And the sensor showed a relatively wide linear range of 1 $fmol \cdot L^{-1}$–35 $\mu mol \cdot L^{-1}$ when used for the detection of furfural in the food industry. Tran et al. [86] prepared a biosensor formed by polyaniline nanowires and AgNPs, showing not only the potential for adhesion to the electrode surface, but also a new electrodeposition and electropolymerization, which was used to detect target DNA with a limit of 2.80×10^{-15} $mol \cdot L^{-1}$. Liu et al. [110] invented a AgNPs EIS biosensor for the determination of *Immunoglobulin E* (*IgE*) in asthma, with a limitation of 1 $pg \cdot ml^{-1}$ and its linear range was from 10 $pg \cdot ml^{-1}$ to 1 $\mu g \cdot ml^{-1}$, which proved that the heavy metal toxicity of silver ions was invalid for certain proteins.

Above we presented metallic singlet nanomaterials attached to enzymes or DNA as sensors, but in fact the catalytic effect of these metallic singlet nanomaterials in an electrochemical environment can also make them a biosensor with a non-enzymatic strategy. Currently, more non-enzymatic sensors based on catalyzed effect that have been studied include noble metal-catalyzed H_2O_2 to monitor H_2O_2 content, and non-precious metal-catalyzed glucose to detect glucose content. Jiménez-Pérez et al. [87] modified a screen-printed carbon electrode with platinum nanoparticles to obtain a biosensor for monitoring H_2O_2 monitoring in living cells with a limit of 24.9 $nmol \cdot L^{-1}$ and a real-time tracking durability for more than 12 h.

Gholami and Koivisto [111] introduced a biosensor based on silver nanoparticles coated with carbon microfibers for the super selective detection of H_2O_2, obtaining two linear ranges of 2.0–10.0 mmol·L^{-1} and 10.0–100.0 mmol·L^{-1} with the limitation of 0.48 μmol·L^{-1}. Wang et al. [88] announced a biosensor for glucose sensing with monolayer and bilayer graphene doped with copper nanoparticles produced by CVD, which has a linear range of 0.02–2.3 mmol·L^{-1}, a determination limit of 1.39 μmol·L^{-1}, *S*/*N* = 3 and high sensitivity with relatively fast response time. Palve and Jha [112] invented a glucose biosensor with copper nanowire–carbon nanotube bilayer, who had a linear range of 10–2000 μmol·L^{-1}, a limit value of 0.33 nmol·L^{-1} and a quick response time within 1 s. Wang et al. [113] reported a biosensor formed with Cu nanoparticles deposited on carbon nanotubes and ferrocene-branched chitosan for the determination of glucose, which performed a broad linear range of 0.2 to 22 mmol·L^{-1}, a limit of 13.52 μmol·L^{-1} and a sensitive limitation of 1.256 μA·mmol^{-1}·L^{-1}·cm^{-1}.

3.2 Metal compound nanomaterials transducers

Metal compound nanomaterials, due to their unique chemistry and physics properties notably, have drew researchers' interests to extend their own crucial share in EIS biosensing. Among all the diversity of metal compound nanomaterials, metal oxides, metal sulfides and metal nitrides are the most eye-catching topics [114–116]. Different from metal simple substance nanomaterials, these three kinds of metal compound nanomaterials show totally opposite properties, which are: (a) relative low conductivity; (b) abundant nanostructures; (c) the diversity of bonding forms and sites; (d) relative high catalysis ability; (e) durability for extreme environment; and (f) considerable compatibility with biomolecules [117–119]. However, because of the disappearance bonding between metal atoms, changes in their crystal structure and the alteration of metal atoms' electrons resulting from the introduction of non-metallic atoms, these three types of metal compounds acquire wide band gaps and become semiconductors or even insulators, and accordingly result in poor ion transport kinetics and unexpected volume change under charging and discharging [118]. Therefore, metal compound nanomaterials are usually compounded with carbon materials, other metal nanomaterials and polymers to obtain synergy for a broad range of applications, as shown in Fig. 7 [114].

Variety of metal oxide nanomaterials have shown their splendid potential to the application of biosensors, including iron oxide, manganese oxide, titanium dioxide, copper oxide, zinc oxide, zirconia, cobalt oxide, nickel oxide, tungsten oxide, vanadium oxide, silver oxide, etc. Some of them have only shown one of the two functions while others have contributed into both two fields, which we will discuss below selectively. For the role of transducer function, Silva and Brett [89] proposed a electrochemical biosensor based on acetylcholinesterase grafted Fe_2O_3 nanoparticles/poly(neutral red) modified electrodes, which acquired a determination limit of 1.04 μmol·L^{-1} for acetylcholine. Xue et al. [120] presented an impedance biosensor rooted in manganese dioxide nanoflowers modified with capture antibodies for *Salmonella typhimurium*, capable of isolating ~ 60% of *Salmonella* from 10 ml samples with its linear range from 3.0×10^1 to 3.0×10^6 CFU·ml^{-1} in 1.5 h and reaching a determination limit of 19 CFU·ml^{-1}. Yu et al. [121] achieved a p-nonylphenol biosensor formed by TiO_2 and polypyrrole, and the linear concentration range of this sensor was from 1.0×10^{-8} to 8.0×10^{-5} mol·L^{-1} with a detection limit of 3.91×10^{-9} mol·L^{-1}. As the role of transducer-catalysis function, Li et al. [122] invented a biosensor using α-Fe_2O_3 nanoparticles to catalyzes the electrooxidation of dopamine, which showed linearity over the dopamine concentration range of 2–80 μmol·L^{-1} and a detecting limit (3 σ/*s*) and sensitivity of 1.15 nmol·L^{-1} and 95.57 μA·μmol·L^{-1}·cm^{-1}. Guan et al. [90] proclaimed a non-enzyme H_2O_2 biosensor with manganese dioxide-graphene nanosheets, which reported with a linear range of 0.5–350.0 μmol·L^{-1}, a determination limit of 0.19 μmol·L^{-1} (*S*/*N* = 3) and a sensitivity of 422.10 μA·mmol·L^{-1}·cm^{-1}. Chen et al. [123] obtained a theophylline electrocatalytic detection biosensor based on rutile-type titanium dioxide microspheres and its decorated graphene oxide, whose linear range accessed from 0.02 to 209.6 μmol·L^{-1}, its limit reached 13.26 nmol·L^{-1}, and sensitivity achieved 1.183 μA·μmol·L^{-1}·cm^{-2}.

Metal sulfide nanomaterials, as one of the representatives of metal compounds, and their diversity demonstrate the potential in biosensors. Binary sulfides, ternary sulfides and quaternary sulfides also have performed both transducer function and catalysis function. For the transducer function, Li et al. [124] announced a biosensor based on multiwalled carbon nanotubes and cobalt(II) sulfide nanoparticles immobilized with glucose oxidase for glucose detection, which had a linear range of 8 μmol·L^{-1} to 1.5 mmol·L^{-1} and a high sensitivity of 15 mA·mol·L^{-1}·cm^{-2}. Giang et al. [55] introduced an EIS biosensor based on PSA antibodies fragments and Cu doped CoS_2/3-phenoxybenzoic acid thin films, which reached a sensitivity of 5.9×10^8 Ω·cm^2·mol·L^{-1} and a detection limit of 3.8×10^{-6} mol·L^{-1}. Negahdary et al. [91] claimed a DNA sensor for the detection of *Aeromonas hydrophila* with ZnS_2 nanospheres, which obtained a range of 1.0×10^{-4} to 1.0×10^{-9} mol·L^{-1} with a detection limit of 1×10^{-13} mol·L^{-1}. For the transducer-catalysis function, Govindasamy et al. [125] invented a biosensor with

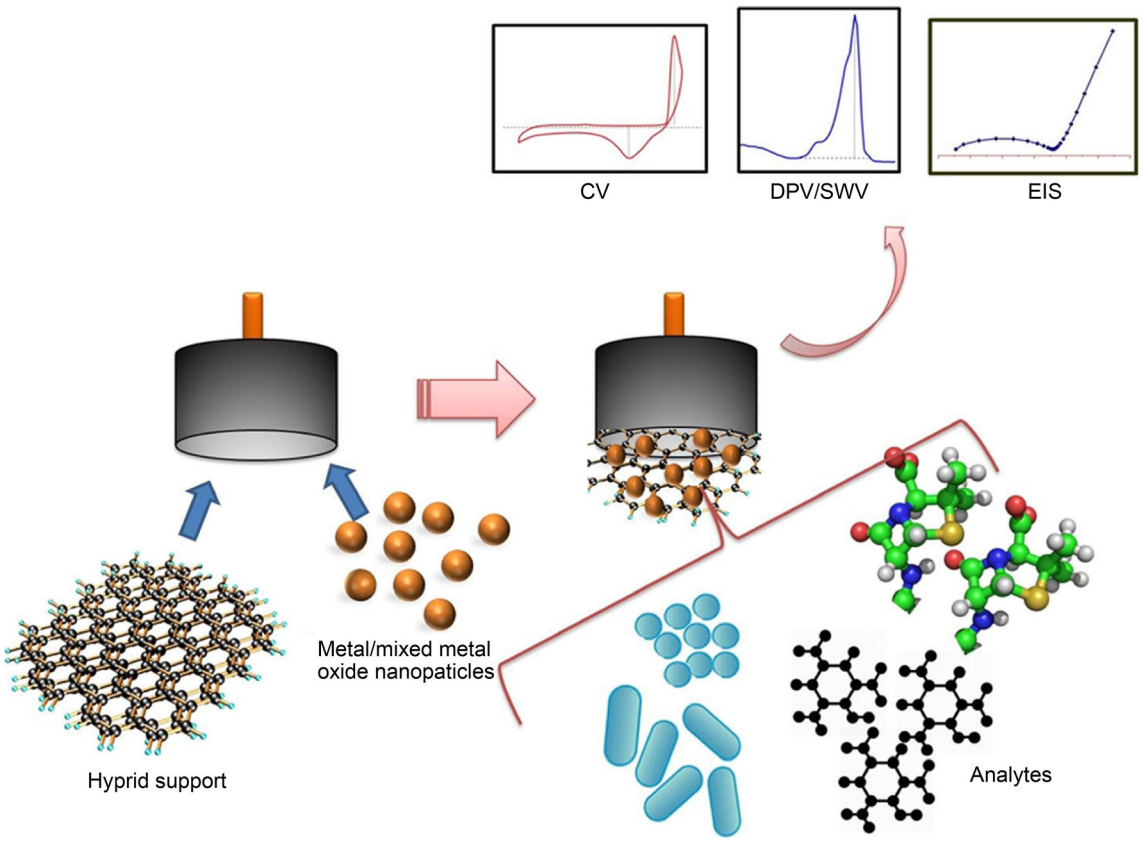

Fig. 7 Schematic representation of metal oxide nanoparticle in electrochemical sensing. Reproduced with permission from Ref. [114]. Copyright 2018, Springer-Verlag GmbH Austria, part of Springer Nature

reduced graphene oxide decorated on Cu_2S nanospheres, which was used for the non-enzymes detection of chloramphenicol with a LOD for chloramphenicol (CAP) of 15.3 nmol·L^{-1}, linear range of 60 nmol·L^{-1} to 1954.5 μmol·L^{-1} and sensitivity of 12.538 μA·μmol·L^{-1}·cm^{-1}. Guo et al. [126] proclaimed a non-enzymatic glucose sensor consisting of $NiCo_2S_4$ nanowire arrays and electrospun graphitic nanofiber films, which achieved a splendid linear range of 0.0005–3.571 mmol·L^{-1} with R^2 = 0.995 and detection limit of 0.167 μmol·L^{-1} with S/N = 3. Zhou et al. [127] reported a Cu_2ZnSnS_4 quantum dot for the non-enzymatic detection of glucose, which was claimed to be the first electrochemical quantum dot on tin oxide glass, and significantly enhanced its remarkable sensitivity from 1561 to 2503 μA·mmol·L^{-1}·cm^{-2}.

Metal nitride nanomaterials are also considered as unrivaled candidates for electrochemical impedance biosensors. Among all the nanomaterials we have discussed, nitride nanomaterials are divided into two categories. One is the field-effect transistor biosensors which are based on the variation of two-dimensional electron gas resulting from the surface environment transforming caused by capture biomolecules, and change their conductance accordingly [128], of which the Group III nitride nanomaterials are the one of the most mentioned and have been extensively reviewed by Li and Liu [116]. Although field-effect transistor biosensors can be regarded as electrochemical biosensors broadly, metal nitride nanomaterials are more representative for their wide application as working electrodes in electrochemical sensing. Regarded it as transducer, Xu et al. [92] proposed a titanium nitride-reduced graphene oxide composite incorporating molecular imprinting for the sensing of bisphenol A (BSA), reaching a linear dependence from 0.5 to 100 nmol·L^{-1} and observing a limitation of 0.19 nmol·L^{-1}. Liu et al. [129] demonstrated a biosensor utilizing the integration of polydopamine (PDA) on the surface of GaN nanowire modified with AuNPs to monitor alpha-fetoprotein (AFP), whose linear range was between 0.01 and 100 ng·ml^{-1}, and its limitation touched downward 0.003 ng·ml^{-1}. Regarded it as a transducer-catalysis function, Chen et al. [130] announced a non-enzyme glucose se^{-1}nsor with nickel nitride-decorated nitrogen-doped carbon spheres through one-pot fabrication, which performed two broad linear ranges from 1 to 3000 μmol·L^{-1} and 3000 to 7000 μmol·L^{-1}, while its high sensitivity was 2024.18 and 1256.98 μA·mmol·L·cm^2, respectively. Rajaji et al. [131] designed a biosensor toward 4-nitroquinoline N-oxide (4-

NQO) using reduced graphene oxide (rGOS) functionalized with iron nitride nanoparticles (Fe_2N NPs), which obtained a broad linear window between 0.05 and 574.2 $\mu mol \cdot L^{-1}$ and a limitation of 9.24 $nmol \cdot L^{-1}$ down to nanomolar level.

3.3 Alloy nanomaterials transducers

Monolithic metals may have shortcomings in sensor applications, so alloyed materials have entered the vision of researchers with their more competitive properties for biosensing. Scientists briefly identified several types of nanoalloys such as: (a) mutual regulation in crystallization [132]; (b) template effect in nanoconstruction [133]; (c) distortion of electron cloud caused by heteroatoms [134] and (d) facultative usage of properties from original component atoms [135]. Therefore, it can be concluded that the interactions between alloy atoms would contribute to enhance the overall effect of the alloy materials to further promote their wide application in the field of biosensors.

Fertilized as transducer function, Lee et al. [93] announced a glucose biosensor consisting of hierarchical Au-Ni alloy and conductive polymer, which attained a linear range from 1.0 $\mu mol \cdot L^{-1}$ to 30.0 $mmol \cdot L^{-1}$ and a determination limit of 0.29 $\mu mol \cdot L^{-1}$. Additionally, they compared the coefficient of variation of enzymatic and non-enzymatic strategies, which obtained 1.82%, $n = 5$ of enzymatic sensors and 2.93% for non-enzymatic sensors. Yadav et al. [136] invented a Pb^{2+} detection biosensor based on the Ag-Au alloy nanoparticles conjugated with aptamer, which led to a linear slope of 0.01–10 $\mu g \cdot L^{-1}$ and minimum detectable Pb^{2+} concentration of 0.8 $\mu mol \cdot L^{-1}$. Song et al. [94] designed several three-dimensional porous bimetallic alloy nanowires compounded and monolayer MoS_2 nanosheet (m-MoS_2) as biosensor for the determination of organophosphate pesticides via acetylcholinesterase inhibition pathway. Among all the candidates, Pd–Ni NWs/m-MoS_2 showed the most stunning outcome, which achieved a linear range from 1×10^{-13} to 1×10^{-7} $mol \cdot L^{-1}$ with a sensitive limitation of 0.05 $pmol \cdot L^{-1}$ under a signal-to-noise ratio of 3.

Fertilized as transducer-catalysis function, Gao et al. [137] claimed a non-enzyme glucose biosensor with in situ assemble of $Ni(OH)_2/TiO_2$ film on NiTi alloy, which reached a sensitivity of 192 $\mu A \cdot mmol \cdot L^{-1} \cdot cm^{-2}$, a determination limit of 8 $\mu mol \cdot L^{-1}$ and a response time of within 1 s. Shim et al. [138] demonstrated a core–shell-structured Au@Pt alloy with particle sizes ranging from 35 to 60 nm, which was further used as a non-enzymatic glucose biosensor to determine glucose in two dynamic ranges of 0.5–10.0 $\mu mol \cdot L^{-1}$ and 0.01–10.0 $mmol \cdot L^{-1}$ with 0.99 as its correlation coefficient and a limit of 445.7 ($\pm$ 10.3) $nmol \cdot L^{-1}$. Li et al. [139] illustrated an amaranth biosensor based on molecularly imprinted Pd-Cu bimetallic alloy modified graphene, which performed a linear relationship with amaranth concentration of 0.006–10 $\mu mol \cdot L^{-1}$ and its limit reached downward 2 $nmol \cdot L^{-1}$ with considerable selectivity.

4 Conclusion and perspective

In conclusion, metal nanomaterials-based EIS biosensors are widely used in medical healthcare, environmental monitoring, and food safety. Bioreceptors and metal nanomaterials are the topic of our demonstration and discussion, which shows multiple strategies to accomplish the feasibility, specificity, sensitivity and simplicity of manufacture and operations for metal nanomaterials-based EIS biosensors. Their respective properties and combined features are exhibited and compared for researchers to form a vivid method library. Our review aims to assist brief acknowledge of current achievement and inspire tremendous innovation in the future.

Although this review summarizes many achievements of metal nanomaterials in the field of electrochemical sensing, the development of electrochemical sensing is still limited, mainly by the current lack of development of metal nanomaterials, including structural limitations and cost constraints. Therefore, we are eager to discuss and witness more breathtaking improvements in the following prospects.

Designing new metallic nanomaterials with secondary structures may lead to a future of nanomaterials with biometric and specificity in terms of structural matching. Metal nanomaterials are designed to have special structural similar to bioreceptors, making them sterically matched. At the same time, the potential complexation and chelation between the target and the metal nanomaterial receptor are utilized to achieve a chemically stable combination and form a secondary structure similar to the direct binding of biological receptors to the target. In this way, the metal nanomaterials receptors can accomplish the receptor and transducer functions.

It is significant to reduce the amount of noble metals to decrease costs, such as the application of single atoms, compounding with materials such as graphene or black phosphorus. The purpose of this design is to completely delegate the function of biological receptors to metallic nanomaterials, while the function of transducers is performed by these non-metallic materials. The non-metallic materials in metal composites tune the electron distribution outside the nucleus of metal nanomaterials and significantly improve their performance as catalysts for biological reactions. Besides, these non-metallic materials have large

specific surface area, low barriers to direct electron transfer with metal nanomaterials, and high electrical conductivity, which are more suitable for application in transducers of biosensors.

Exploring more non-precious metals such as manganese, cadmium, nickel, etc. to replace the existing precious metals is also an avenue for biosensor development. Biosensors based on manganese, cadmium, and nickel nanomaterials have been discussed in this paper and have been used in biosensors in various fields. However, a major limitation that they have not yet been used on a large scale is that their chemical properties are too active, and the fabricated biosensors cannot have long-term stability. Therefore, these non-noble metal nanomaterials need to be treated to maintain their catalytic activity without degrading them, such as coating with carbon nanotube cages.

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Declarations

Conflict of interests The authors declare that they have no conflict of interest.

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