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REVIEW ARTICLE

Biosensors and nanobiosensors for rapid detection of autoimmune diseases: a review

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Abstract

This review (with 77 refs.) describes the progress that has been made in biosensors for the detection of autoimmune diseases, mainly via detection of autoantibodies. In addition, specific proteins, cytokines and ions have also been introduced as promising diagnostic biomarkers. Following an introduction into the various kinds of autoimmune diseases, we first discuss the state of the art in respective electrochemical biosensors and nanobiosensors (with subsections on amperometric, impedimetric, voltammetric and photoelectrochemical methods). The next large chapter covers optical methods (with subsections on electrochemiluminescence, fluorescence and surface plasmon resonance). We then make a critical comparison between commercially available kits used for detection of autoimmune diseases with the established biosensors. Several Tables are also presented that give an overview on the wealth of methods and nanomaterials. Finally, in the conclusion part, we summarize the current status, addresse present issues, and give an outlook on potential future opportunities.

Keywords Biosensor · Nanomaterial · Autoantibodies · Sensing · Biomarkers

Introduction

Autoimmune diseases include various chronic disorders which are classified as either organ-specific (e.g., thyroid diseases, Graves' disease, type 1 diabetes, and primary biliary cirrhosis) or systemic (e.g., antiphospholipid syndrome, rheumatoid arthritis, and systemic lupus erythematosus) [1]. These disorders usually occur due to the loss of normal immunological self-tolerance leading to high-affinity autoantibodies formation which mistakenly attack to own body' cells, tissues and organs [2–4]. Autoimmune diseases may affect only about 8% of the population [5], however, they are one of the major causes of severe disability, organ failure and mortality, forcing high medical expenses [3]. Therefore, early diagnosis of these disorders shares a high degree of importance to improve the patients' quality of life.

Autoantibodies (AAbs) in clinical samples can be applied as the best diagnostic biomarkers to predict the onset, development and severity of the autoimmune disorders. Because they can be detected several years before the emergence of clinical manifestations and irreversible damages [6, 7]. Moreover, autoantibodies are very useful and valuable markers because of their specificity and stability during the illnesses [8]. Currently, Enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF) and western blotting are the most common traditional methods which have been developed for AAbs detection in autoimmune disorders [3, 9]. However, these techniques are expensive, time-consuming, and inconvenient needing sophisticated instruments. Furthermore, the sensitivity of these traditional methods is not satisfactory. Because they are often able to diagnose an autoimmune disease when irreversible tissue damages have

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occurred [3, 10]. Considering these limitations, development of novel and reliable techniques for AAbs detection is very important in early diagnosis of autoimmune diseases.

Biosensors are among the most promising approaches for detection of diseases-related biomarkers because of their capability in rapid, sensitive, label-free, cost-effective and real-time detection [11]. A biosensor is an integrated receptor–transducer device which can be selectively used for quantitative or semi-quantitative analytical detection [12, 13]. Depending on their signal transducer type, biosensors can be designated as optical, electrochemical and piezoelectric systems [14]. Nanomaterial (NMs) are potential candidates used in fabrication of biosensors for increasing their sensitivity and lowering the detection limits (LOD) [15].

In addition to AAbs, some proteins [16, 17], chemokines [18], cytokines [19], cells [20], and ions [21] have also been found as promising biomarkers for autoimmune diseases diagnosis or monitoring. A list of common autoimmune diseases and related biomarkers are presented in Table 1. Considering the advantages of biosensors, in this review we will discuss about various electrochemical and optical biosensors and NMs-based biosensors (nanobiosensors) developed so far for detection of autoimmune diseases.

Electrochemical methods

Electrochemical devices are the most common biosensors used for early detection of disease-related biomarkers because of their sensitivity, selectivity, cost-effectiveness and rapid response [22]. In addition, these biosensors have gained a great deal of interests as appropriate small platforms for point-of-care (POC) tests. Various electrochemical biosensors and nanobiosensors have been reported in the literature for different biomarkers detection in autoimmune diseases using mostly amperometric, impedimetric and voltammetric techniques (Table 2).

Table 1 Examples for autoimmune diseases and associated biomarkers

Autoimmune disorder	Common biomarker
Systemic lupus erythematosus	Anti-dsDNA, Anti-ribonucleoprotein
Celiac disease	Anti-tTG, AGA, anti-DGP, Gluten
Rheumatoid arthritis	ACPAs, Anti-CCP, Anti-TNF-α
Multiple sclerosis	Anti-MBP, MMP, Anti-CSF114(Glc)
Antiphospholipid syndrome	Anti-phospholipid
Hashimoto thyroiditis	TSH, Anti-TPO
Diabetes mellitus type I	Glucose, Anti-GAD, Insulin
Sjögren syndrome	Anti-ribonucleoprotein, anti-SSA
Chronic autoimmune hepatitis	Anti-SLA
Graves'disease	Anti-TSH

Anti-dsDNA, anti-double stranded DNA; anti-tTG, anti-tissue transglutaminase; AGA, anti-gliadin AAbs; anti DGP, anti-deamidated gliadin peptide; ACPAs, anti-citrullinated peptide AAbs; anti-CCP, anti-cyclic citrullinated peptide; Anti-TNF-α, anti-Tumor necrosis factor-α; anti-MBP, anti-Myelin Basic Protein; MMP, Matrix metalloproteinase; TSH, Thyroid-stimulating hormone; anti-TPO, anti–thyroid peroxidase; anti-GAD, anti-glutamic acid decarboxylase; anti-SSA, anti-Sjogren's syndrome A; anti-SLA, anti-soluble liver antigen

Amperometric methods

Amperometric biosensors measure the produced current to determine the quantity of an analyte with a fixed potential [53]. Fagúndez et al. (2018) designed a sandwich-format electrochemical immunosensor for anti-double stranded DNA (anti-dsDNA) autoantibodies assay in serum samples of patients with systemic lupus erythematosus (SLE). The detection limit of this platform was 8 $\mu g.mL^{-1}$ via using amperometric detection method [23]. In another study by Villa et al. [30], an amperometric immunosensor was fabricated for anti-citrullinated peptide antibodies (ACPAs) assay as potential biomarker for diagnosis of rheumatoid arthritis (RA). Multiwalled carbon nanotube–polystyrene (MWCNT–PS) composite were applied for development of the platform sensitivity. Li et al. (2008) also designed an amperometric nanobiosensor based on gold nanoparticles, titanium dioxide nanoparticles and thionine (NGP-NTiP-Thi) for detection of macrophage migration inhibitory factor (MIF) in serum of RA patients. This immunosensor was reported to be highly specific for MIF with a LOD of 0.02 $ng.mL^{-1}$ and linear range from 0.03 to 230 $ng.mL^{-1}$ [31].

Electrical impedimetric methods

Electrical impedance spectroscopy (EIS) biosensor is a powerful and nondestructive technique which has recently been increasingly used as diagnostic tools [54]. In a study by Wilson et al. (2015) a label-free EIS immunosensor has been employed for detection of anti-transglutaminase (anti-tTG) antibodies in patients with celiac disease. For increasing the efficiency and biocompatibility, they employed a platinum modified polypyrrole-cobalt (II) salicyladiimine metallodendrimer nanocomposite. A linear range of 10^{-5} – 10^{-4} $mg.mL^{-1}$ and the LOD of 201 $ng.mL^{-1}$ was achieved for this platform [33]. Singh and coworkers also developed a label-free nanogap-interdigitated electrode (IDE) biosensor for quantitative detection of anti-tTG antibodies. The sensitivity of this novel sensing platform was improved using gold nanoparticles (AuNPs) and the dynamic detection of that was in the range of 30 pM to 30 nM using EIS [35]. In another study conducted by Derkus et al. (2013), a label-free electrochemical impedance immunosensor was fabricated for the determination of anti-myelin basic protein (anti-MBP) autoantibodies in multiple sclerosis (MS) patients. Taking the

Table 2 Electrochemical biosensors and nanobiosensors application in autoimmune diseases

Detection method	Biomarker	Biofluid	Nanomaterial	Limit of detection (LOD)	Linear range (LR)	References
Amperometric	Anti-dsDNA	Serum	_	0.8 μg.mL^{-1}	_	[23]
Amperometric	Anti-tTG (IgA)	Serum	AuNPs	1.7 AU.mL^{-1}	0–30 AU.mL^{-1}	[24]
Amperometric	Anti-tTG (IgG)	Serum	AuNPs	2.7 AU.mL^{-1}	0–30 AU.mL^{-1}	[24]
Amperometric	Anti-tTG	Serum	_	390 ng.mL^{-1}	_	[25]
Amperometric	Anti-tTG	Serum	_	0.26 μg.mL^{-1}	0.26 to 6.9 μg.mL^{-1}	[26]
Amperometric	AGA	Serum	_	46 ng.mL^{-1}	0–1000 ng.mL^{-1}	[27]
Amperometric	AGA	Serum	_	20 ng.mL^{-1}	0 to 750 ng.mL^{-1}	[28]
Amperometric	AGA	Spiked serum	_	33 ng.mL^{-1}	0 to 10 μg.mL^{-1}	[29]
Amperometric	AGA	Spiked serum	_	135 ng.mL^{-1}	0 to 10 μg.mL^{-1}	[29]
Amperometric	AGA	Spiked serum	_	240 ng.mL^{-1}	0 to 10 μg.mL^{-1}	[29]
Amperometric	AGA	Spiked serum	_	250 ng.mL^{-1}	0 to 10 μg.mL^{-1}	[29]
Amperometric	ACPAs	Serum	MWCNT–PS composite	_	_	[30]
Amperometric	MIF	Serum	AuNPs/NTiP-Thi	0.02 ng.mL^{-1}	0.03 and 230 ng.mL^{-1}	[31]
Amperometric	L-cysteine	Urine	PdNPs/rGO/Nafion	0.15 μM	0.5 to 10 μM	[32]
EIS	Anti-tTG	_	Platinum modified polypyrrole-cobalt (II) salicyladiimine metallodendrimer composite	201 ng.mL^{-1}	10^{-5}–10^{-4} mg.mL^{-1}	[33]
EIS	Anti-tTG	Serum	AuNP/OPPy	5.2 ng.mL^{-1}	10^{-6}–10^{-4} mg.mL^{-1}	[34]
EIS	Anti-tTG	Serum	Pr-A-AuNPs	_	30 pM to 30 nM	[35]
EIS	Anti-MBP	Serum and CSF	_	0.1528 ng.mL^{-1}	0.975 to 2500 ng.mL^{-1}	[36]
EIS	Anti-MBP	Serum and CSF	TiO2 nanoparticles	0.1495 ng.mL^{-1}	0.4875 to 2500 ng.mL^{-1}	[36]
EIS	IL-12	Serum	_	1.0 pg.mL^{-1}	0 to 100 pg.mL^{-1}	[19]
EIS	IL-12	Serum	_	3.5 pg.mL^{-1}	3.75 to 7.5 pg.mL^{-1}	[37]
EIS	MMP-9	Plasma	_	15 ng.mL^{-1}	50 to 400 ng.mL^{-1}	[38]
EIS	Zinc	Serum	_	100 fM	1 pM to 100 nM	[21]
EIS	Copper	Serum	_	500 fM	1 pM to 100 nM	[21]
CV	Anti-tTG	Serum	MWCNTs/AuNPs	_	_	[39]
CV	AGA (IgA)	Serum	MWCNTs/AuNPs	9.1 U.mL^{-1}	_	[40]
CV	AGA (IgG)	Serum	MWCNTs/AuNPs	9.0 U.mL^{-1}	_	[40]
CV	anti-DGP	Serum	MWCNTs/AuNPs	_	_	[41]
CV	Anti-tTG	Serum	MWCNT/AuNP/GQD/PAMAM	50 fg.mL^{-1}	_	[42]
CV	Anti-CSF114(Glc)	Serum	_	_	_	[43]
DPV	Anti-tTG	Serum	WCNT/AuNP/GQD/PAMAM	20 fg.mL^{-1}	_	[42]
DPV	Anti-tTG	Serum	CdSe/ZnS QDs	2.4 U.mL^{-1}	3 to 100 U.mL^{-1}	[44]
DPV	Anti-tTG	Serum	QDs	1.0 U.mL^{-1}	3 to 40 U.mL^{-1}	[45]

Table 2 (continued)

Detection method	Biomarker	Biofluid	Nanomaterial	Limit of detection (LOD)	Linear range (LR)	References
DPV	Anti-tTG	Serum	CdSe/ZnS QDs	2.2 $U.mL^{-1}$	0 to 40 $U.mL^{-1}$	[46]
DPV	MBP	Serum	GO/pPG nanocomposite	0.30 nM	58 to 227 nM	[17]
DPV	Tau	CSF	GO/pPG nanocomposite	0.15 nM	0.5 to 15.1 nM	[17]
DPV	TNF-α	Serum	AuHCF/AuNPs	5.5 $pg.mL^{-1}$	10 $pg.mL^{-1}$ to 40 $\mu g.mL^{-1}$	[47]
LSV	TSH	Serum	–	0.012 $mIU.L^{-1}$	0.02 to 100 $mIU.L^{-1}$	[48]
SWV	Insulin	Serum	PGE/MWCNT-pyrenyl nanostructures	15 pM	0 to 100 pM	[49]
SWV	anti-TG2	Serum	Graphite–epoxy composite	–	–	[50]
PEC	FLS cell	–	ZnO NRs/CH3NH3PbI3/NCQDs nanocomposites	2 $cell.mL^{-1}$	1.0×10^4 to 10 $cell.mL^{-1}$	[20]
PEC	TNF-α	Serum	GO/PTCNH2	3.33 $pg.mL^{-1}$	10 to 100 $ng.mL^{-1}$	[51]
PEC	IL-6	Serum	LaFeO3 nanoparticles/FTO	33 $fg{\cdot}mL^{-1}$	0.1 $pg{\cdot}mL^{-1}$ to 0.1 $\mu g{\cdot}mL^{-1}$	[52]

advantages of titaniumdioxide (TiO2) nanoparticles, a LOD of 0.1495 $ng.mL^{-1}$ with 0.4875–2500 $ng.mL^{-1}$ detection range were achieved for this EIS based biosensor [36]. Another label-free EIS based immunosensor was fabricated for MS diagnosis by detection of Interleukin-12 (IL-12) as a serum cytokine. The LOD of this sensitive biosensor was calculated to be as 3.5 $pg.mL^{-1}$ [37].

Voltammetric methods

Voltammetric biosensors includes different methods such as cyclic voltammetric (CV), differential pulse voltammetry (DPV), linear sweep voltammetry (LSV), and square wave voltammetry (SWV). As demonstrated in Table 2, they are among the most widely used and available methods for sensitive detection of specific biomarkers in different autoimmune diseases due to their high sensitivity, selectivity, cost-effectiveness and ability of simultaneous quantification of their targets. Gupta and colleagues have developed a GQD/PAMAM nanohybrid modified AuNP embedded in MWCNT based nanobiosensor for early determination of anti-tTG antibodies in human celiac disease (Fig. 1). This ultrasensitive biosensor can detect the biomarker as low as 50 and 20 $fg.mL^{-1}$ by CV and DPV techniques, respectively [42]. Neves et al. (2012) designed another CV based nanoimmunosensor for detection of anti-tTG antibodies in serum of the patients. They immobilized human tTG on screen-printed carbon electrode modified with carbon nanotubes and AuNPs which was a trustful analytical tool for celiac disease diagnosis [39]. Recently, Derkus et al. (2017) have reported a novel nanoimmunosensor based on graphene oxide (GO)/[poly(propyleneglycol)] (pPG) nanocomposite for the simultaneous detection of MBP and Tau proteins in cerebrospinal fluid (CSF) and serum samples of MS patients. DPV detection revealed a reliable and sensitive detection with a LOD of 0.30 nM and 0.15 nM and linear range of 58–227 nM and 0.5–15.1 nM for MBP and Tau proteins, respectively [17]. One another group developed an indirect electrochemical magneto immunosensor for anti-transglutaminase enzyme (ATG2) assay in serum samples of patients with celiac disease. First, the TG2 was covalently immobilized on magnetic beads (MBs) and following addition of ATG2, the Peroxidase-labeled antibody (anti Ig–HRP) was incorporated for the revelation and the analytical signal was detected by SWV [50].

Photoelectrochemical methods

Photoelectrochemical (PEC) is another detection method which has gained a lot of attention due to its high sensitivity, simplicity, low background signals and fast response [13]. Pang et al. (2016), have recently synthesized a PEC biosensor based on ZnO nanorods (NRs)/CH3NH3PbI3/nitrogen-doped carbon quantum dots (NCQDs) nanocomposites for rapid determination of fibroblast-like synoviocyte (FLS) cells as

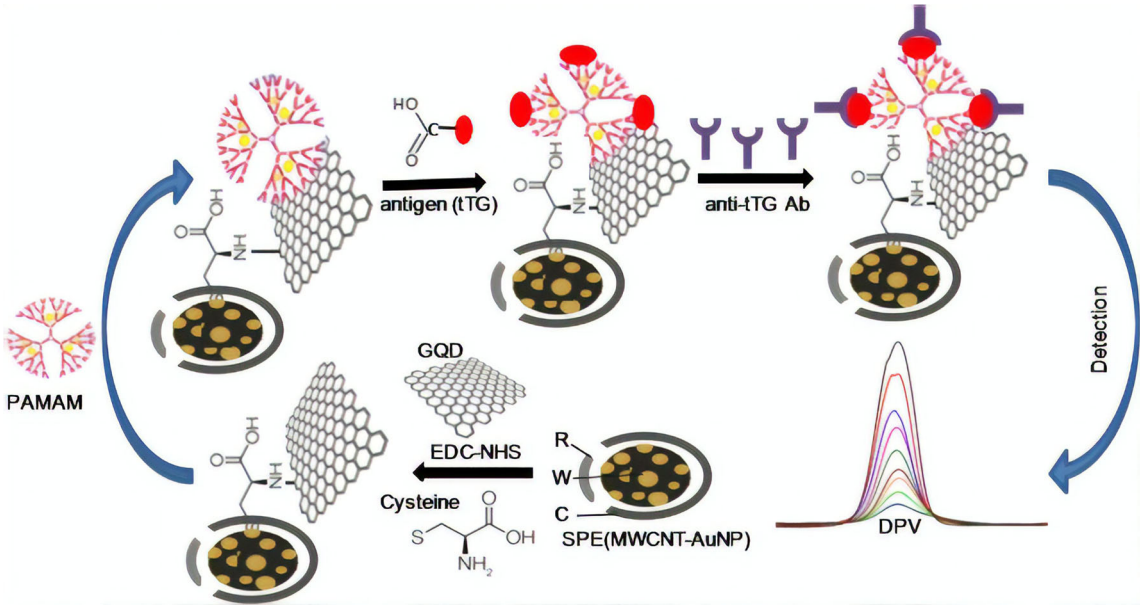

Fig. 1 Schematic representation of a cyclic voltammetry nanobiosensor based on GQD/PAMAM nanohybrid modified AuNP embedded in MWCNT for early detection of anti-tTG antibodies in human celiac disease. Reprinted with permission from (Gupta et al.,2017)

significant biomarkers for early diagnosis of RA (Fig. 2). The nanobiosensor provided a great analytical device for FLS cells assay with an LOD of 2 cell.mL^{-1} and linear range of 10^4 to 10 cell.mL^{-1} [55].

Brief overview of electrochemical methods

Overall, electrochemical biosensors, especially amperometry and voltammetry based platforms, are the most frequent methods used for detection of autoimmune disorders. Reusable and rapid detection capability, requirement of low sample volume, Easy miniaturization, and feasibility of quantitative analysis are several advantages of these techniques [56, 57]. However, there are also limitations related to these techniques including false positive results originated from matrix electrolytes and inadequate control on the working electrode at higher currents [57]. As demonstrated in Table 2, these methods also achieved LODs as low as fg. mL^{-1} range which is contributed to early stage diagnosis and management of autoimmune diseases.

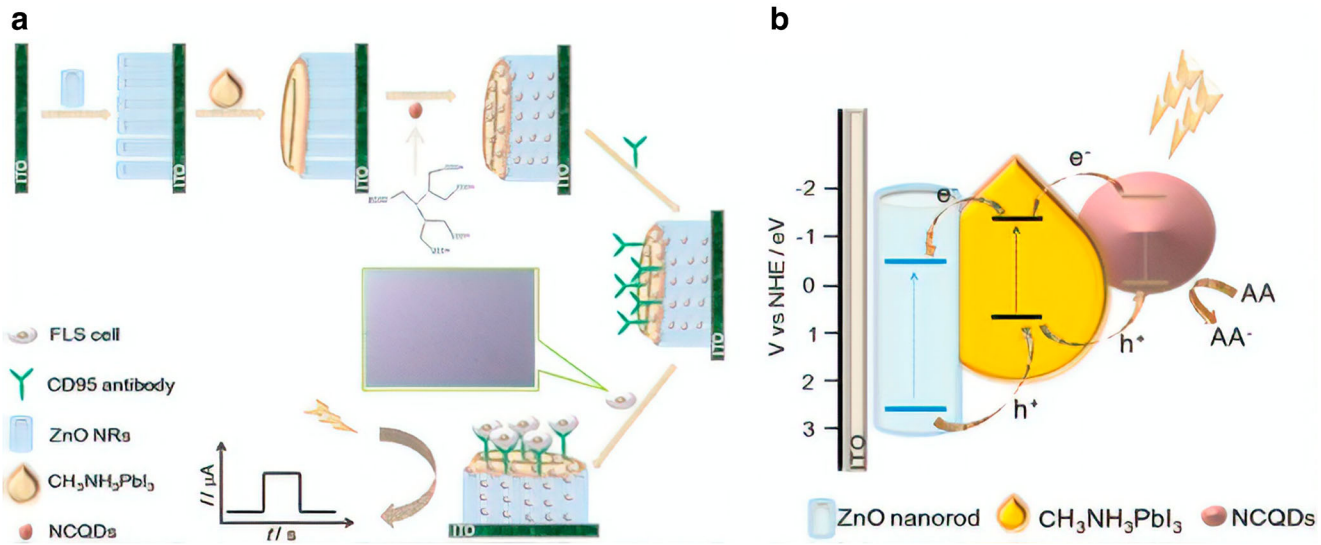

Fig. 2 **(a)** Schematic representation of a photoelectrochemical biosensor based on ZnO NRs/CH3NH3PbI3/NCQDs nanocomposites for detection of FLS cells in RA disease and **(b)** schematic illustration of the energy level diagram. Reprinted with permission from (Pang et al., 2016)

Table 3 Optical biosensors and nanobiosensors application in autoimmune diseases

Detection method	Biomarker	Biofluid	Nanomaterial	Limit of detection (LOD)	Linear range (LR)	References
ECL	Anti-tTG	Serum	Membrane-templated gold NEEs	0.5 ng.mL^{-1}	1.5 to 10,000 ng.mL^{-1}	[58]
ECL	Anti-CCP	Serum	g-C3N4@PANI-Au	0.2 pg.mL^{-1}	0 to 15 ng.mL^{-1}	[59]
ECL	Anti-GAD	Serum	AuNPs	0.1 ng.mL^{-1}	0.3 to 50 ng.mL^{-1}	[60]
Fluorescent	microRNA-145	Serum	silver nanoclusters (NC)	0.1 nM	0.1 to 1.6 nM	[61]
Fluorescent	Anti-CCP	Serum	_	_	_	[62]
SPR	Anti-GAD	Serum	_	_	3.3×10^4 to 2.6×10^5 ng.mL^{-1}	[63]
SPR	Anti-GAD	Serum	AuNPs	0.03 ng.mL^{-1}	~100 ng.mL^{-1}	[64]
SPR	Anti-tTG	Serum	_	_	30–3000 nM	[65]
SPR	Gluten	Urine	_	0.33 ng.mL^{-1}	1.12 to 19.20 ng.mL^{-1}	[66]
SPR	Anti-CSF114(Glc)	Serum	_	_	_	[67]
SPR	CXCL12	Urine	_	_	5–40 nM	[18]
SPR	Anti-TNF-α	Plasma	_	0.093 μg.mL^{-1}	_	[68]
SPRi	Anti-hnRNP A2/B1	Serum	_	_	_	[69]
SPRi	Anti-hnRNP A2/B1	Serum	_	_	_	[69]
SPRi	Anti-hnRNP A2/B1	Serum	_	_	_	[69]
SPRi	microRNA-422	Serum	nGNSs	0.55 pM	_	[70]
SPRi	microRNA-223	Serum	nGNSs	0.88 pM	_	[70]
SPRi	microRNA-126	Serum	nGNSs	1.19 pM	_	[70]
SPRi	microRNA-23a	Serum	nGNSs	1.79 pM	_	[70]

Optical methods

Optical biosensors are intriguing options for screening of biomarkers in medical diagnostics which offer advantages of label-free detection [53]. Recently, the diagnosis and monitoring of various autoimmune diseases has undergone extreme modifications via optical biosensors. Table 3 summarizes the studies which conducted on the use of optical biosensors or nanobiosensors such as electrochemiluminescence (ECL), fluorescence, surface plasmon resonance (SPR) and surface plasmon resonance imaging (SPRi) for detection of specific biomarkers in biofluid samples of patients with different autoimmune diseases. Additionally, a number of representative examples of theses biosensors will be discussed in the next parts.

Electrochemiluminescence

Due to their remarkable advantages such as sensitivity, rapid response, wide detection range and simple controllability, ECL sensors are widely used for detection purposes [71, 72]. Zhao et al. constructed a label-free ECL immunosensor based on asymmetric heterogeneous polyaniline-gold (PANI-Au) nanomaterial for highly sensitive quantification of anti-cyclic citrullinated peptide antibody (anti-CCP) for RA early diagnosis. To form the sending platform, PANI-Au nanomaterial was incorporated with graphite-like carbon nitride (g-C3N4) which improved the stability, ECL efficiency of g-C3N4 and facilitated CCP immobilization on electrode (Fig. 3). As reported, the biosensor accounted for a low limiting detection of 0.2 pg.mL^{-1} in the concentration range of 0–15 ng.mL^{-1} [59]. In another study [58], a novel ruthenium (Ru)-based ECL immunosensor was designed for anti-tTG assay in celiac disease via gold nanoelectrode ensembles (NEEs). The authors reported a linear range between 1.5 ng.mL^{-1} and 10 μg.mL^{-1} and a LOD of 0.5 ng.mL^{-1}.

Fluorescence

Fluorescence detection is another common optical method wieldy used for development of biosensors. In a recent study, Mansourian et al. (2017) [61] reported a nanobiosensor based on fluorescent DNA hosted silver nanoclusters (AgNCs) and hybridization chain reaction (HCR) amplification for determination of microRNA-145 as a biomarker in MS patients' plasma. AgNCs have taken great attention due to their features

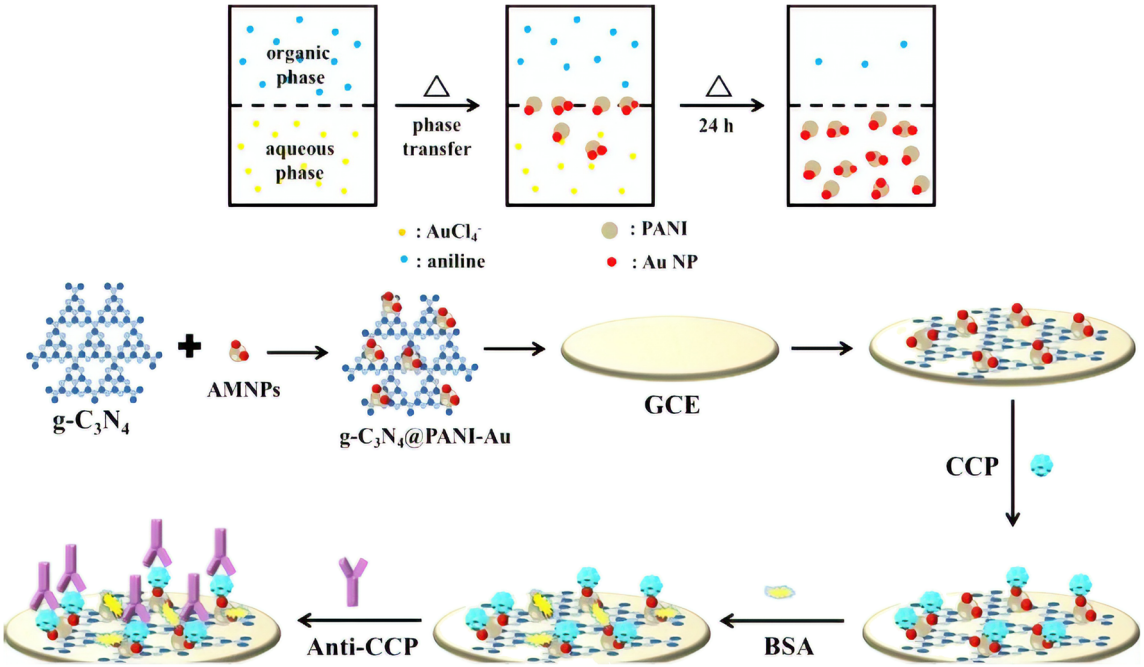

Fig. 3 Schematic representation of an ECL immunosensor based on PANI-Au nanomaterial for early detection of anti-CCP in RA disease. Reprinted with permission from (Zhao et al., 2018)

such as low toxicity, biocompatibility, simple synthesis, water solubility and high photostability [73]. This biosensor has the excellent ability to detect 0.1 nM of microRNA-145.

SPR/SPRi

SPR biosensors have become popular for molecular interactions measurements and have a wide variety of applications as diagnostic devices [11]. A SPR biosensor was fabricated by Vega et al. (2013) for real-time detection of chemokine CXCL12 in urine samples of RA patients. CXCL4 was incorporated into lentiviral particles (LVPX4) and coupled covalently to the SAM-coated gold chip via amine coupling. The sensitive biosensor showed a detection range of 5–40 nM [18]. In another experiment, Cennamo and colleagues employed a plastic optical fibers (POF) based SPR biosensor for anti-tTG autoantibodies quantification in celiac disease with a 30 to 3000 nM detection range [65].

Recently, Sguassero et al. (2019) developed an enzyme-free strategy for the simultaneous multiple microRNAs assay in blood of patients with MS via single nanostructured enhancer of SPRi. Neutravidin-coated gold nanospheres (nGNSs) were functionalized with biotinylated antibody against DNA/RNA hybrids and four microRNAs were detected with a LOD of up to 0.5 pM (Fig. 4) [70].

Brief overview on optical methods

In general, optical based biosensors have remarkable advantages like ability of quantitative analysis with no need for any advanced tools [56]. SPR biosensors are one of the most common optical methods used for detection of autoimmune diseases because of their sensitivity, specificity, cost-effectiveness and label-free detection capability [14]. Furthermore, pathogenic potential of several autoimmune diseases have revealed to be associated with the affinity of different autoantibodies subtypes and binding characteristics [74, 75]. Therefore, application of SPR biosensors, which can evaluate binding characteristics and kinetic parameters, can be more reliable than traditional laboratory tests for diagnosis and management of autoimmune disorders. However, the interaction between coexisting biomarkers in human real samples limit the use of SPR biosensors for specific biomarker assay in autoimmune disorders. Besides, according to the reported LODs, the ECL based biosensors exhibited high sensitivity for detection of autoimmune diseases, whereas the SPR method had the lowest sensitivity.

Comparison of commercial kits used for detection of autoimmune diseases with the established biosensors

Antibody-based colorimetric assay methods such as ELISA are the most available commercial kits for diagnosis of autoimmune diseases (Table 4). Antibody-based assay techniques have several restrictions such as need for high-priced antibodies, long incubation periods, large volume of sample, complicated instruments and procedures [76, 77]. Moreover, in comparison with the ELISA kits, biosensors showed improved

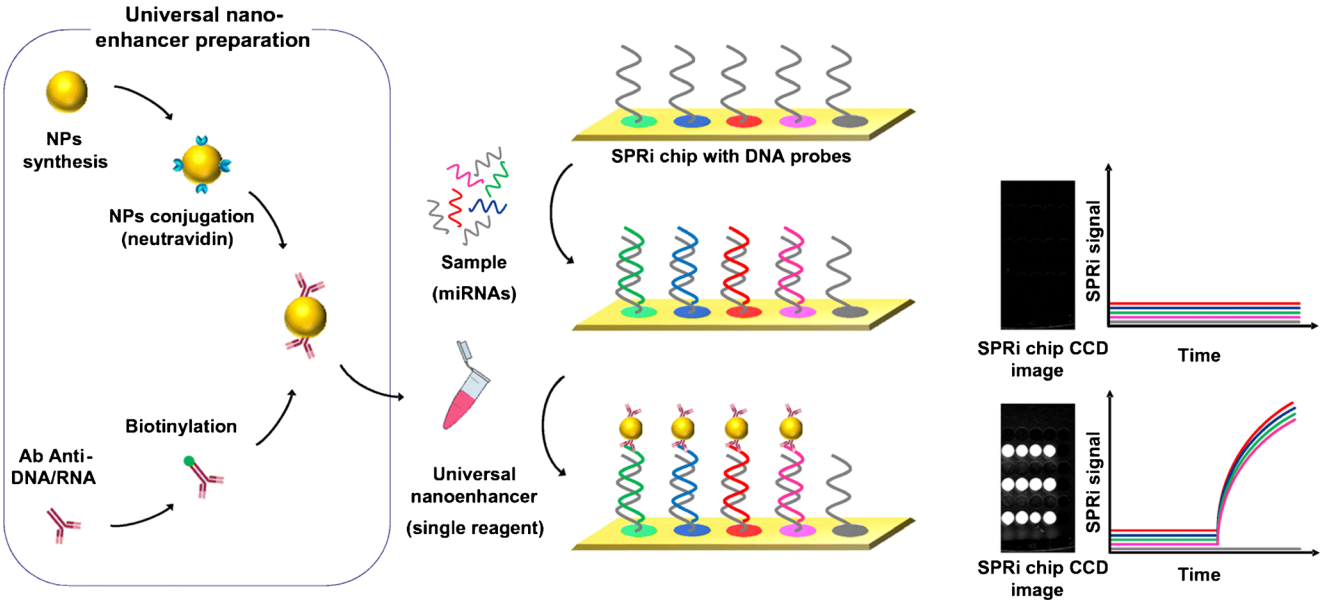

Fig. 4 Schematic representation of the strategy used for the simple and simultaneous detection of multiple microRNAs in MS patients using single nanostructured enhancer of SPRi. Reprinted with permission from (Sguassero et al., 2019)

sensitivity and LOD for detection of autoimmune diseases. Therefore, they can be used as potential devices for point-of-care (POC) in the future of clinical diagnostics.

Conclusion and future perspectives

There is an increased demand for highly sensitive analytical techniques for detection of trace quantity of biomarkers in the early stages of autoimmune disorders to prevent from permanent organ failures. Over the past decade, many efforts have been made to develop various biosensors for rapid and sensitive detection of AAbs or other biomarkers related to autoimmune diseases. Unique advantages of biosensors over traditional assays including high sensitivity, low-cost, rapid, reliable and real-time detection have made them suitable options for detection of different biomarkers in autoimmune diseases. However, despite great advances in the development of biosensors for effective detection of autoimmune diseases, much effort is still required to introduce them as an appropriate technique for POC diagnostics. NMs integration with biosensing platforms is an appropriate signal amplification method which have remarkably enhanced their sensitivity. Accordingly, the nanobiosensors have reached LOD in the picomolar and femtomolar range which is providing novel strategies in early stage diagnosis of autoimmune diseases

Table 4 Comparison of analytical performance of numerous commercial kits for detection of autoimmune diseases

Commercial kit	biomarker	Assay sensitivity	Assay range	Sample types	Detection method	Assay time
antibodies-online	Anti-dsDNA	3.75 IU/mL	6.25–400 IU/mL	_	Colorimetric	_
Eagle Biosciences	Anti-tTG	1 U/mL	1–300 U/mL	Serum, plasma	_	2 h, 30 min
Biomatik	Anti-tTG	0.094 ng/mL	0.156–10 ng/mL	Serum, plasma, tissue homogenates, and other biological fluids	Colorimetric	–
LifeSpan Biosciences	Anti-TG2	_	0.625–40 ng/mL	Tissue homogenates	Colorimetric	4 h, 30 min
Arigo	ACPA	1 U/mL	20–1.000 U/mL	Serum, plasma	Colorimetric	30, 15, 15, 5 min
Mybiosource	AGA	0.5 AU	100–1.56 AU	Serum, plasma or cell culture supernatants	_	_
antibodies-online	Anti-MBP	1.56 ng/mL	1.56–100 ng/mL	_	Colorimetric	_
USCN	Anti-MBP	1.28 ng/mL	3.12–200 ng/mL	Serum, plasma and other biological fluids	Colorimetric	2 h, 30 min

in vitro and in vivo. However, the biosafety of NMs must be regarded in use of nanobiosensors for in vivo detection of autoimmune disease. In addition, since the most of the biosensors have been employed for in vitro quantification of biomarkers, further effort is needed for development of sensing platform for detection of autoimmune diseases in vivo. Taken together, with the great advancement in biosensor technique, remarkable progress in these sensing platforms with potential diagnostic features are expected to occur in the future.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

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