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Review

Biosensors for autoimmune diseases

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ABSTRACT

Diagnosis of autoimmune diseases (ADs) is usually based on symptoms and laboratory tests that measure the occurrence of serological and genetic biomarkers such as peptides, autoantibodies, and complement proteins. Early detection of AD is essential to reduce the severity of symptoms and organ damage as a result of progressive disease. Biosensors are tools that convert biochemical signals produced by molecular elements into optical, electrical, and other physical signals for analysis. In recent years, peptides, antigens, aptamers, autoantibodies, and other biomolecules have provided suitable diagnostic features for development of biosensors in detecting and follow up the diagnoses and treatment of diseases. This study reviews the introducing of different biomarkers in ADs with the novel vision to use of biosensor technology for research and development in this regard. Therefore, this study has the required innovation for using biosensor technology with more attention to electrochemical based biosensors to developing, targeting and designing the easy applicable and available diagnostic and response to treatment products using key biomolecules for ADs. It will help readers to understand the research trends of biosensors in ADs and further advance the development of this paramount field.

1. Introduction

Autoimmune diseases (ADs) are defined as dysfunctions of the body's immune system, which lead to loss of tolerance to self-antigens, causing the formation of autoantibodies and damage to body organs, cells, and tissues [1]. AD is usually associated with chronic diseases and complications. The high death rate caused by ADs imposes a heavy financial burden on the society, which leads to a significant threat to life and a decrease in the quality of life in people [2]. Classification of AD includes the chronic and heterogeneous disorders categorized as either organ-specific (e.g., thyroid diseases, Graves' disease, diabetes mellitus type 1, and primary biliary cirrhosis) and systemic disorders (e.g., antiphospholipid syndrome, rheumatoid arthritis, and systemic lupus erythematosus) [3]. Common ADs are systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes, systemic sclerosis (SS), pemphigus vulgaris, inflammatory bowel disease (IBD), Hashimoto's disease, rheumatoid arthritis (RA), Behcet's disease and antiphospholipid syndrome (APS) [4–6]. Although, each AD is unique, they all result from intolerance to self-antigens [7]. Today, new methods have emerged to identify the molecules involved in the onset and progression of the disease. Biosensor development can be used to create a strong scientific foundation for the development of personalized medicine and various other fields. Current methods are laboratory-based and require trained personnel for operation. Finding new methods to achieve early diagnosis and prognosis of AD is essential to control disease progression. A biosensor system for early detection usually includes: a biomarker (target molecule), bio-receptor (recognition element), and a well-suited bio transducer. Biosensors are presented as promising technology to follow-up the progression of disease. Also, they have been introduced to identify biomarkers in cancer and cardiovascular diseases. Biomarkers such as peptides, antigens, aptamers, and autoantibodies can reveal biological processes in the course of AD [8]. Therefore, there is an urgent need to find and introduce biomarkers involved in the pathogenesis of different types of ADs. Fundamental problems in

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differential diagnosis of various types of autoimmune diseases with similar sign and symptoms, unclear etiology and the lack of a specific and optimal diagnostic method with convenient, cheap and accessible device for patients and physician are one of the major concerns of the scientific community. The main desire of this study was to draw the attention of scientists to the presence and role of biosensor technology, with various advantages and greater ease, for the early diagnosis of autoimmune diseases. This is a step towards creating a contribution considered significant in the scientific community. The purpose of this study is to review the use of biosensor technology for biomedical research and development in ADs.

2. Autoimmune diseases and biomarkers

2.1. Biomarkers in Myasthenia gravis (MG)

Myasthenia gravis (MG) is principally triggered by autoantibodies to postsynaptic nicotinic acetylcholine receptors (AChRs). These autoantibodies that cause muscle weakness and fatigue, have been inhibited with RNA aptamers. The RNA aptamers with 2′-amino pyrimidines and 2′-fluoro pyrimidines inhibited rat monoclonal antibodies (mAb198) specific to the significant immunogenic region of the human acetylcholine receptors (AChRs). Both 2′-amino and 2′-fluoro RNA aptamers had a sequence of 89 nucleotides. The 2′-fluoro RNA had a better binding affinity [9]. This suggests that a single aptamer may be generated from two different libraries in the standard systematic evolution of ligands by exponential enrichment (SELEX). These aptamers showed high serum stability, inhibit antibody-AChRs interactions, and cross-reactions with autoantibodies from MG patients. It was shown that an RNA aptamer inhibited both monoclonal antibody that recognizes the major immunogenic region on the AChR, and MG patient autoantibodies to modulating AChRs on human cells [10]. The chemical construction of aptamers became more accessible by optimizing the structure of these small molecules. Thus, secondary structure, binding region analysis, and site-directed mutagenesis were performed on a 2-fluoro modified 89 nucleotide sequence [11]. The reduced version of the aptamer with 47 mer was able to effectively protect cells against the effects of autoantibodies and can even be used to treat MG [12]. These aptamers may be considered potential MG therapeutic options due to these promising findings.

2.2. Biomarkers in rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is most frequent autoimmune arthritis with unknown etiology, which affects about 0.5 % to 1.0 % of adults worldwide. RA, a long-term autoimmune disorder, produces a progressive inflammatory response that mainly leads to severe pain, swelling, and stiffness in the joints of the limbs [13]. Early detection of RA can prevent joint erosion. Researchers developed an electrochemical nanobiosensor for immediate recognition of RA biomarkers, and anti-cyclic citrullinated peptide antibodies, using molybdenum disulfide (MoS2) polyaniline (PANI) as the base matrix of the screen-printed electrode and with PANI-Au nanomatrix which was able to detect RA biomarker in human serum [14]. Researchers accurately determined 100-fold diluted serum samples from RA patients through an amperometric biosensor with magnetic microbeads modified with a biotinylated-anti-dsDNA to effectively capture serum autoantibodies [15]. The amperometry at screen-printed carbon electrodes using hydroquinone/hydrogen peroxide was the earliest immunosensor for simultaneous detection of CXCL7 chemokine and MMP3 metalloproteinase as biomarkers for RA with the limits of 0.8 ng mL^{-1} (CXCL7) and 1.2 pg mL^{-1} (MMP3) [16]. MicroRNAs (miRNAs) are a collection of short non-coding RNAs that play critical regulatory roles in cells. Due to the clinical significance of miRNA and the inherent benefits of optical sensors, it was reported that the use of a fiber optic sensor based on Lossy Mode Resonance (LMR) for the detection of miRNA hsa-miR-223 is a promising biomarker for the diagnosis of RA [17]. Researchers examined the expression profiles of circular RNAs (circRNAs) in the PBMCs of RA patients by RNA sequencing. They showed the aberrant dysregulation of circRNAs, including hsa_circ_0000396 and hsa_circ_0130438, in RA patients. They suggested the prospective diagnostic value of circRNAs for the diagnosis of RA and also the advantage of RNA sequencing versus microarrays for screening differentially expressed circRNAs [18]. Studies have also demonstrated that circRNAs such as, hsa_circ_0044235 was decreased in PBMCs of RA patients, while hsa-miR-892a expression was increased [19]. Using the avidin–biotin bio-recognition system, the electrochemical immunosensor by the anti-cyclic citrullinated peptide antibody was developed for diagnosis of RA in human serum [20]. Similarly, another peptide-based sensor was developed using electrochemical impedance spectroscopy and confirmed by an ELISA method that can detect autoantibodies in RA [21]. Also, it has been demonstrated that simultaneous determination of rheumatoid factor and anti-cyclic citrullinated peptide autoantibodies in human serum by a dual electrochemical biosensor, could be performed about four times less than that required for the ELISA method [22]. Further, to monitor the initiation and progression of synovial tissue inflammatory responses in patients with arthritis, a three-dimensional synovium-on-a-chip was developed with non-invasive optical light-scatter biosensing [23]. The main symptom of RA is joint pain and deformity caused by chronic synovial inflammation, which leading to joint destruction and disability. Several biomarkers indicate a poor prognosis, with the quick distraction of the joints, in the event of a positive serum test: high acute phase reactants (erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) tests. Other (non-specific) biomarkers for RA include tumor necrosis factor (TNF), interleukin 6 (IL-6), osteopontin, osteocalcin, amino-terminal telopeptide of type 1collagen, carboxyl-terminal telopeptide of type 1 collagen, and matrix metalloproteinase 3 [24–27].

2.3. Biomarkers in systemic lupus erythematosus (SLE)

SLE is a chronic-complex autoimmune disease with variable manifestations which causes significant morbidity and mortality. It affects 40 to 50 people per 100,000 with a female-to-male ratio of 9:1. Determination of the SLE-specific autoantibodies simplifies the SLE diagnosis [28]. Researchers developed giant magneto resistive (GMR) biosensor microarrays to recognize the interferon-associated autoantibodies with the chemokine score [29]. The autoantigens, including histones H2A and H4, H2B, and H3, Ribo P, dsDNA, U1-70 K, Ro52, Ro60, La/SSB, and Smith, were analyzed by robotic contact microarray for SLE diagnosis [29]. Human vascular cell adhesion molecule-1 was introduced as a reliable urinary biomarker for SLE, evaluated by non-redox electrochemical assay technology [30]. An amperometric magnetic bead-based biosensor was developed to monitor antibodies against aquaporin-4. This platform was implemented to analyze serum samples from healthy individuals and patients with SLE and Alzheimer's disease, offering advantages in terms of cost and point of care [31]. Long noncoding RNA (LncRNA) has been shown to promote SLE by increasing the expression of complement factor H-related protein 5 and degrading miR-222 [32]. Since T cells play a vital role in the etiology of SLE, researchers studied the regulatory mechanism of circRNA in T cells of SLE patients. They found that a circRNA–miRNA–mRNA regulatory system comprising of 8 circRNAs, 4 overlap miRNAs, and 13 target mRNAs has a regulatory role in T cells of SLE patients [33]. MiR-125a expression levels were reduced in juvenile-onset SLE patients compared to normal controls. Further, plasma levels of IL-17 and IFN-γ in SLE patients were significantly greater than in healthy people. They suggest that MiR-125a could act as a candidate therapeutic target for regulating inflammation in SLE patients [34]. Researchers reported that interleukin-16 (IL-16) is involved in the RA and SLE pathogenesis and evaluated the association between rs1131445 polymorphism in the IL-16 gene with risk and clinical characteristics of RA and SLE in the Iranian population [35].

Also, immunofluorescence tests are routinely used for detecting anti-dsDNA (α-dsDNA) antibodies, a serological marker, in blood samples of SLE patients [36,37]. Recently, electrochemical biosensors have been used for rapid and easy detection of α-dsDNA antibodies for diagnosis and monitoring of autoimmune diseases [38]. On the other hand, specific antibodies have been suggested as a treatment option in various diseases [39,40]. The researchers developed a new Igβ and FcγRIIB cross-linking antibody called ASP2713. It was able to bind to B cells and induce intrinsic negative feedback signals, suggesting that ASP2713 could be used to treat SLE, where B cells play a pathogenic role [41]. In conclusion, SLE patients may benefit from using the binding ability of a mouse anti-DNA IgG monoclonal antibody-aptamers to recognize and/or neutralize anti-DNA autoantibodies.

2.4. Biomarkers in multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic and inflammatory disorder of the central nervous system characterized by progressive neurodegeneration [42]. Indeed, the central nervous system CNS's chronic, autoimmune, demyelinating disorder characterized by oligodendrocytes and myelin sheath damage by abnormal infiltration of immune cells: T- cells, B-cells, and macrophages [43]. The prevalence of MS is 30 cases per 100,000 people, and the prevalence of this disease in women is three times that of men [44]. In some studies, the role of microRNAs as a biomarker in MS patients has been mentioned [45,46]. It was reported that in cell-free cerebrospinal fluid, levels of miR-21 and miR-146a/b may represent treasured biomarkers for identifying patients with dynamic MS lesions [47]. A study looked at the function of B cells and T cells in regulating microRNA expression in MS patients [48]. In a study, to identify miR-155 as a biomarker in MS patients, they used a biosensor that included carbon nanotubes and polypyrrole on a graphite sheet [49]. To determine anti-myelin basic protein autoantibodies, a relevant biomarker in MS patients, an amperometric platform with carboxylated magnetic microparticles was developed. In terms of sensitivity and range of linearity, that method for the detection of autoantibodies showed better performance and shorter assay time compared to commercially available ELISA kits [50]. The high level of anti-nuclear antibodies (ANA) as an immunological epiphenomenon in patients with MS and, also in chronic viral hepatitis such as hepatitis C virus (HCV) patients has the possibility of differentiation using functional biosensors. The development of a lateral flow biosensor based on gold nanoparticles or RT-LAMP-AuNPs-LFB has provided a low-cost, high-sensitivity and rapid detection biosensor for visual detection of HCV, which is potentially applicable for clinical procedure [51,52]. In such a subgroup of patients, novel biosensor-based technology could improve their clinical management. Recently, scientists found hepatitis B antibodies in clinical saliva of patients via high sensitive plasmonic hepatitis B biosensor and nanoparticle-based lateral flow biosensors with loop-mediated isothermal amplification [53,54]. The use of plasmonic enhanced fluorescence sandwich immunoassay provides a satisfactory, non-invasive, rapid and specific detection of biomolecules and molecular biomarkers in patient samples in systemic diseases [53].

2.5. Biomarkers in celiac disease (CD)

Celiac disease (CD), one of the most common AD diseases, is caused by the consumption of wheat gluten and similar proteins in barley and rye, which trigger an autoimmune response that causes atrophy and hyperplasia of the small intestine. CD is a chronic gluten-induced autoimmune disorder that typically damages the lining of the small intestine in genetically predisposed individuals. Patients should follow a lifelong gluten-free diet. Diagnosing CD is somewhat difficult due to its multifaceted manifestations in patients. Currently, CD diagnosis is usually based on serological tests for serum antibodies such as anti-transglutaminase antibody (anti-TGA), blood test of high concentration of protein with considerable sensitivity and specificity for CD. In previous studies, the high diagnostic accuracy of blood test for anti-transglutaminase IgA (tTG) autoantibodies compared to antigliadin and antiendomysium assays for monitoring and diagnosing patients with CD was confirmed, which is a challenging issue in terms of sensitivity and specificity. The positive results in CD patients was confirmed by using recombinant human tTG antibody method and this test was suggested for CD diagnosis screening [55]. Novel bionsensor-based technology could be of clinical-diagnostic utility with detecting the serological biomarkers like recombinant human tTG antibody specially by electrochemical immunosensors, the useful tool for determining positive and negative CD serum samples, and provide the non-invasive sensitive, selective, and stable biomarker sensing technique for CD's diagnosis [56,57]. Recently, analytical tools such as immunosensors based on nanoelectrode arrays have been used. Researchers have developed a portable device in which electrochemical signals are generated and processed through an integrated IoT-WiFi board sharing the results over the cloud by physicians or caregivers. The electrochemical platform consisted of screen-printed electrodes that functioned with AuNPs, and transglutaminase was fixed on it to capture anti-TGA. The amperometric signal was generated via a secondary Antibody labeled with alkaline phosphatase (AP) [58]. Biosensors have been considered a promising way to perform techniques in biomarker sensing, where electrode materials and architecture playcritical roles in achieving sensitive and prompt detection [56,59]. Researchers introduced three circulating miRNAs (miR-192-5p, miR-215-5p, and miR-125b-5p) as non-invasive biomarkers for diagnosing CD patients with a low TGA-IgA titer the adherence to a gluten-free diet in a cohort of pediatrics CD [60,61]. As an immunosensor assay in CD patients, the nano structured electrochemical sensor was described to detect IgA isotypes of anti-tissue transglutaminase, which provided a low detection limit of human serum samples from celiac patients [62]. Since the exact cause of the CD has not been determined, a recent study examined the role of different genes and microRNAs (miRNAs) in patients with CD [63]. A study in children with CD showed increased expression of miRNA-21 and decreased expression of miRNA-31 in the serum of celiac patients and demonstrated that circulating miRNA-21 and miRNA-31 could serve as potential non-invasive biomarkers in pediatric patients [64]. The expression of inflammation-related miRNA-146a, miRNA-155, miRNA-21, and miRNA-125b increases in peripheral blood. Those miRNAs were involved in immune processes, suggesting they could be considered potential diagnostic biomarkers for CD [65].

2.6. Biomarkers in Behcet's disease (BD)

Behcet's disease (BD) is a chronic, relapsing, systemic vasculitis of unfamiliar etiology with clinical features and cardiac involvement [66]. BD and its related disorder Sweat disease are multisystem inflammatory conditions defined by muco-cutaneous symptoms. Recent advances in microfluidic, microelectronic, and electrochemical measurement methods have paved the way for developing of potential biosensors in healthcare monitoring. Sweat components could serve as promising biomarkers for non-invasive health monitoring [67]. Researchers considered vascular endothelial growth factor (VEGF) in clinical tears in order to detect and monitor diabetic retinopathy and used an electrochemical reusable aptasensor for quantitative detection of VEGF. Their platform was based on hybridization chain reaction, CeO_2 nanoparticles, and strand displacement reaction. They suggested that the ultrasensitive aptasensor could be used for non-invasive screening of diabetic retinopathy in clinical tears [68]. It was reported that serum microRNA-146a expression was significantly higher in Egyptian BD patients than in controls [69]. It was shown that Th17 cells and Th17-related cytokines were increased in Behcet's patients, while regulatory T cells (Treg), interleukin 10 (IL-10) levels and expression of forkhead box P3 messenger RNA (mRNA) were decreased [70]. Recent reports concluded that miRNA-499 expression and IL17 levels were significantly higher in BD patients than in healthy controls [71]. Researchers stated that miR-

20a, miR-34a, miR-197, U6snRNA, miR-205, miR-222, miR-296, miR-302a, miR-302c, and miR-372 were detected up-regulated in BD, while miR-518b, and miR-874 were down-regulated in BD patients [72]. Accordingly, the immune cells assessment and the relevant miRNA profile may serve as a prognostic biomarker and therapeutic approach in BD patients. Table 1 shows biomarkers used for diagnosis of autoimmune diseases.

3. Application of biosensors in autoimmune diseases (ADs)

3.1. DNA based biosensor

Cell-based biosensors are genetically engineered living cells that are applied to detect specific biomarkers. Researchers developed a viable CHO-K1 cell line that expressed both a chimeric thyroid stimulating hormone receptor (TSHR-Mc4) and a luciferase-based cAMP biosensor capable of detecting anti-TSHR autoantibodies in Graves' disease [73]. With the advances in this field, there are challenges that pose barriers to increasing cell-based biosensor applications [74]. In electrochemical biosensors, the main biomarker is developed based on DNA (E-DNA) biosensors, which utilize DNA oligomers covalently bound to an electrode surface. These oligomers are usually subjected to a conformational change in the target-bound vs. the unbound state. By attaching a redox-active molecule (e.g., methylene blue) to the oligomer, this conformational change altered the electron transfer kinetics with the electrode surface, creating a measurable difference in current. Researchers designed and examined an E-DNA biosensor to detect Celiac disease (CD) autoantibodies. In this approach, attaching CD-specific autoantibodies to a synthetic epitope causes a conformational change in the biosensor and a difference in the environment of a fixed redox reporter, which produces a measurable current reduction [75]. When a cell's DNA is damaged and cellular homeostasis is disturbed, DNA sensors, which are DNA-binding proteins as a component of the innate immune system, may sense the disturbance and initiate intracellular signaling cascades of the innate immune system as an active response (Fig. 1). Having such responses is important during viral infection because induction of interferons (IFNs) is a potent immune response that acts both autocrinely and paracrinely to induce antiviral immunity in the host [76]. During exposure to the virus, immunity against it is done with the help of IFNs. Type I IFNs regulate viruses in infected cells and prevent them from spreading to surrounding cells. DNA sensors induce not only type I IFN production, but also induce programmed cell death as part of the body's innate immune response to infection [77]. The host must distinguish between viral and its own DNA to activate appropriate innate responses against viral infections. The signaling specificity of DNA sensors is attributed to various factors, including (a) length and 3D structure of cytotoxic DNA molecules; (b) the subcellular localization of DNA molecules; (c) the methylation status of DNA molecules; and (d) the association of histones and nonhistone chromatin-binding proteins with cytotoxic DNA molecules [78]. There are two broad groups of innate immune DNA sensors based on how they are expressed and found in the body. The first group comprises of endosomal DNA sensors, like members of the TLR family. These TLRs are located on the endosomal membrane of many immune cells, including macrophages, dendritic cells (DCs), and B cells. They look inside lysosomes and endosomes for cytotoxic DNA, such as bacterial and viral DNA, which can harm to the body. The second group comprises the cytosolic DNA sensors, which can detect cytoplasmic nucleic acids in almost all types of cells [77].

Table 1
Autoimmune diseases: Biomarkers and Symptoms.

Disease/condition	Biomarkers	Symptoms
Systemic lupus erythematosus	Anti-dsDNA, Anti-Ro/SSA, anti-La/SSB, Antinucleosome, Anti-C1q, Anti-NMDA-R, Anti-CRP, Antiinterferon-α	Hemoptysis, Acute pneumonitis, Weakness, paralysis, bilateral sensory deficit, impaired sphincter control, Seizures,
Neuropsychiatric SLE, antiphospholipid syndrome	Anti-N-methyl-D-aspartate receptor (NMDA-R), anti-ribosomal P antibodies, antiphospholipid antibodies	Encephalopathy, psychosis, focal central nervous system disease
Systemic vasculitis	Anti-PR3, Anti-MPO, Anti GBM	Pain after eating, double vision, shortness of breath, Bleeding under the skin
Myasthenia gravis	Anti AChR and muscle-specific receptor tyrosine kinase (MuSK) antibodies	Weakness, breath, and swallowing problems
Scleroderma	Anti-Scl-70; ANA, anti-centromeres, anti-RNA Polymerase III	Raynaud syndrome, polyarthralgia, skin tightening, and contractures of the fingers
Systemic sclerosis	Anti-topoisomerase I	Renal crisis
Behcet's syndrome	Sedimentation rate or C-reactive protein may be elevated, and Anticardiolipin antibodies are present in as many as 30 % of patients	Colicky abdominal pain, Recurring genital sores, Eye inflammation, Skin sores
Rheumatoid arthritis	anti-cyclic citrullinated peptide (anti-CCP), RF, Anti-drug (adalimumab)	Pain, stiffness, swelling of joints, Airflow obstruction, Red, painful, and photophobic eye
Antiphospholipid syndrome	Anti-phospholipid antibodies	DVT, pulmonary thromboembolism, fetal loss, retinal artery occlusion, Thrombocytopenia, Anemia, leukopenia
Dermatomyositis, polymyositis	Anti-Jo-1, other myositis-specific autoantibodies	Progressive symmetric muscle weakness, dysphagia, dysphonia
Wegener's granulomatosis	Anti-neutrophil cytoplasmic antibodies (ANCA, MPO, or PR3)	Mucopurulent rhinorrhea, subglottic stenosis, hypopharyngeal ulcerations
Goodpasture's syndrome	Anti-GBM, MPO-ANCA, PR3-ANCA	Pulmonary hemorrhage, acute renal failure
Relapsing polychondritis	Anti-type II collagen	Stridor, laryngotracheal strictures
Sjogren's syndrome	anti-Ro (SS-A) and anti-La (SS-B) antibodies, rheumatoid factor (RF), and antinuclear antibodies	Unusual weakness, marked bilateral parotid gland enlargement

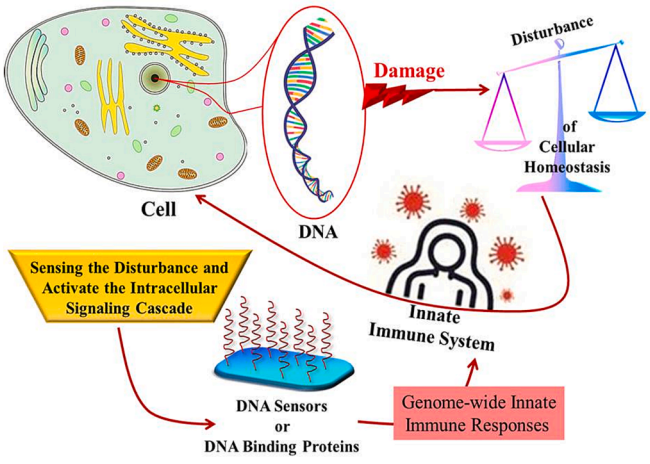

Fig. 1. DNA sensors for sensing the disturbance in cell homeostasis and activation of the intracellular signaling cascades of the immune system. DNA sensors are DNA-binding proteins as the element of the innate immune system for genome-wide innate immune responses.

3.2. Peptide-based biosensors

The capacity of peptides to self-assemble into highly ordered 1D, 2D, and 3D structures makes them one of the most versatile tools in creating flexible scaffolds. Peptides may be used as bioreceptor (recognition unit), due to their ability to modify their secondary configuration by changing the amino acid sequence or by optimizing the interaction between adjacent peptides. Short peptides can be easily synthesized using simple, rapid, and inexpensive techniques. They have good biocompatibility, chemical and structural stability superior to proteins and offer short response time in electrochemical detection. Peptide-based biosensors are expected to be useful tools in bioassays and pave the way for advanced biomolecular systems and challenging analyses [21,40]. By using these biomolecules, a new option for diagnosis and treatment of AD is provided. Autoantibodies and specific biomolecules that are found in different systemic autoimmune diseases can be used for developing different types of biosensors (Fig. 2). Also, the epitope vaccine candidate was designed using B and T-cell epitopes that can act as an immunogen and provoke immune response in the host immune system [79]. Immunosorbent biosensor assay platform is comfortable and less expensive than ELISA test. After the partial tranquility due to vaccines, serious issues can be concluded for future control of the same epidemic. Therefore, more studies are needed to design new vaccines to control Ads.The sensitivity of a specific protein domain can be increased by combining a multi-epitope vaccine with a nanobiosensor array chip [80]. By using anti-human IgG on the surface of the nanobiosensor chip, the multi-epitope vaccine is more effective and is recognized faster by the immune system. This method allows rapid evaluation of vaccine effectiveness on a large scale. Recent research has introduced the use of the nanoplasmonic immunosorbent assay platform as a high-throughput platform to evaluate the effectiveness of vaccines [81]. The epitope information could help in developing an effective vaccine against special pathogens. The use of biomarkers is a promising approach to identify, classify and treat patients with AD. Various autoantibodies with different specificities have been found in AD; some are associated with multiple diseases and some are disease-specific, allowing their use as diagnostic biomarkers [82]. Since autoantibodies are a type of diagnostic biomarkers in ADs, relevant biosensors are mainly designed based on antigen–antibody interactions. Transducers used in biosensors can be optical, magnetic, mechanical and electrochemical. Therefore, this study has the required innovation for using biosensor technology with more attention to electrochemical based biosensors, because of its ease of use and affordability, to developing, targeting and designing the easy applicable and available diagnostic and response to treatment products using key biomolecules for ADs.

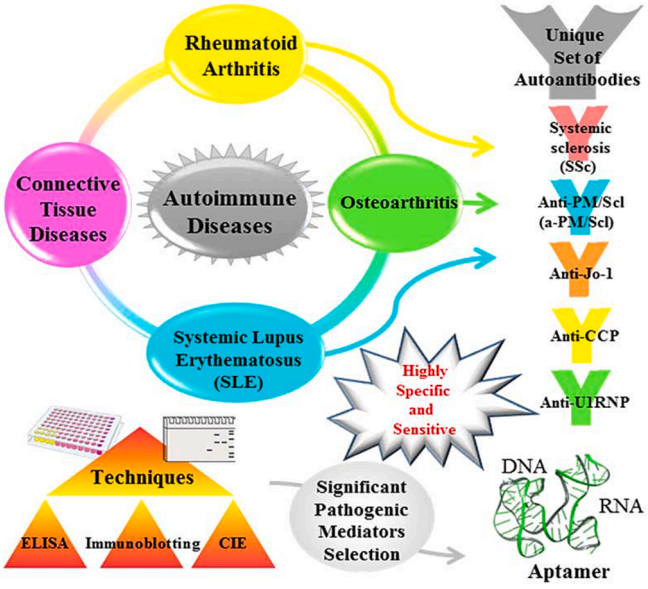

Fig. 2. Autoantibodies and specific biomolecules that are found in different systemic autoimmune diseases can be used as biosensor development. (Anti histidyl tRNA synthetase (anti-Jo-1), Anti-U1-ribonucleoprotein (anti-U1RNP), systemic sclerosis (SSc) autoantibodies, Anti-cyclic citrullinated peptide (anti-CCP) antibody, Anti-PM/Scl antibodies, counter immunoelectrophoresis (CIE) test, Enzyme-linked immunosorbent assay (ELISA).

4. Conclusion and future perspectives

AD occurs when the immune system produces inflammatory molecules and antibodies that mistakenly attack its own body. Today, it is widely believed that ADs are caused by the interaction between environmental and genetic factors. In particular, under the influence of environmental factors such as ultraviolet radiation, chemical compounds, and infectious agents, self-tissue antigens of vulnerable persons may be exposed, which elicits autoimmune responses. Then, the production of large numbers of cytokines and auto-antibodies causes damage to certain tissues. At present, AD is often diagnosed after apparent symptoms, and the treatment strategy is only to relieve symptoms rather than cure. The use of biosensors as biological detectors provides facilities for accurate monitoring of disease status and evaluation of drug response in clinical trials. In this regard, biomarkers can indicate pathogen-induced inflammation and AD status. Old-style diagnosis of autoimmune disease is mainly based on physician evaluation along with basic laboratory tests. But, these checks are not sensitive enough to identify early molecular actions, and often, it is too late to control these ADs and turn tissue damage out when conventional tests show positivity for disorder.

It should be noted that biosensors still suffer from limitations, including complex and time-consuming manufacturing steps, high cost, lack of application on real samples, and error during measurement. Hence, they need advance developments in terms of the simplicity of the production steps, cost-effectiveness, multiple detection ability, and their application to existent samples. Advances in biotechnology in the past decades help to determine new biomarkers along with a suitable strategy for designing biosensors that can be used in the diagnosis of one disorder. In this study, we reviewed the progress in the development of biosensor-based approaches and related tools for monitoring of biomarkers related to some ADs. The use of biosensor technology could be a promising way to identify specific biomolecules for diagnosis, targeted therapy and drug response tracking.

5. Authorship contribution statement

The concept or design of the article (YP, EDA, SRS, EF and FF), Manuscript preparation (OY, YP, EDA, SRS, EF and FF), Figures and Tables (ASh, and FF), Drafted the article or revised it (OY, YP, EDA, SRS, EF and FF); Approved the version to be published (OY, YP, EDA, FF, SRS, EF and ASh).

CRediT authorship contribution statement

Omid Yeganeh: Writing – review & editing, Validation, Investigation, Conceptualization. **Elaheh Dalir Abdolahinia:** Writing – original draft, Validation, Investigation, Conceptualization. **Saeideh Razi Soofiyani:** Writing – original draft, Validation, Investigation, Data curation. **Elnaz Faghfuri:** Writing – original draft, Validation, Investigation. **Abbas Shafie:** Software, Formal analysis. **Yasamin Pahlavan:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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