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The Role Of Laboratory Tests In Diagnosing Autoimmune Diseases

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Abstract

Autoimmune diseases (ADs) are characterized by the immune system's malfunction, leading to the production of autoantibodies and subsequent damage to tissues, cells, and organs. The diagnosis of ADs remains challenging due to their multifaceted clinical manifestations and the lack of optimal diagnostic methods. Recent advancements in biosensor technology have introduced novel techniques for identifying molecules implicated in the onset and progression of these diseases. This review aims to emphasize the role of biosensors in the early diagnosis of ADs, focusing on their applications in the biomedical study of specific conditions such as myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, celiac disease, and Behcet's disease. The study highlights the potential of various biomarkers, including autoantibodies, microRNAs, and circulating RNAs, in unveiling the biological processes during the course of ADs. DNA-based and peptide-based biosensors are discussed as promising tools for detecting these biomarkers, offering advantages such as cost-effectiveness, rapid response times, and improved sensitivity. The review also explores the challenges associated with biosensor technology, including complex manufacturing processes, high costs, and limitations in analyzing real-world samples. Future perspectives emphasize the need for advancements in simplifying production, enhancing

cost-effectiveness, enabling multiplex detection, and expanding applicability to real-world samples. The integration of biosensor technology could revolutionize the identification of specific biomolecules for diagnosing ADs, enabling targeted therapies and effective tracking of drug responses.

KEYWORDS: Laboratory Tests, Autoimmune Diseases, Diagnosis, Immunological Testing, Antibody Testing, Blood Tests.

1. Introduction

Autoimmune diseases (ADs) are characterized as malfunctions in the immune system that lead to the loss of tolerance to self-antigens. This results in the production of autoantibodies and subsequent damage to tissues, cells, and organs (Kryssia et al., 2018). ADs are often chronic in nature and are associated with numerous complications. These diseases significantly increase mortality rates, impose substantial economic burdens, and negatively affect the quality of life. ADs are classified into organ-specific disorders, such as thyroid diseases, Graves' disease, type 1 diabetes, and primary biliary cirrhosis, and systemic disorders, including antiphospholipid syndrome, rheumatoid arthritis, and systemic lupus erythematosus (SLE). Common autoimmune diseases include SLE, multiple sclerosis (MS), type 1 diabetes, systemic sclerosis (SS), pemphigus vulgaris, inflammatory bowel disease (IBD), Hashimoto's thyroiditis, rheumatoid arthritis (RA), Behçet's disease, and antiphospholipid syndrome (APS). Despite their diversity, all ADs share a fundamental mechanism involving self-antigen intolerance (Moritz et al., 2020).

Recent advancements have introduced novel techniques for identifying molecules implicated in the onset and progression of these diseases. One promising area is the development of biosensors, which are crucial for advancing personalized medicine and related fields. Traditional diagnostic methods are laboratory-based and require specialized personnel, underlining the need for innovative approaches to facilitate early diagnosis and prognosis of ADs. A typical biosensor system for early detection comprises a biomarker (target molecule), a bio-receptor (recognition element), and a compatible bio-transducer. Biosensors are emerging as valuable tools for tracking disease progression and identifying biomarkers in conditions like cancer and cardiovascular diseases. Specific biomarkers, such as peptides, antigens, aptamers, and autoantibodies, play a pivotal role in unveiling biological processes during the course of Ads (Pahlavan et al., 2019).

There is an urgent necessity to identify biomarkers involved in the pathogenesis of different ADs. The differential diagnosis of ADs with overlapping signs and symptoms, their uncertain etiology, and the lack of optimal diagnostic methods pose significant challenges. Thus, developing convenient, cost-effective, and accessible diagnostic tools is a pressing concern within the scientific community. This study aims to emphasize the role of biosensor technology, with its numerous advantages and ease of use, in the early diagnosis of ADs. The objective is to contribute meaningfully to scientific discourse by reviewing the applications of biosensor technology in the biomedical study of autoimmune diseases.

2. Autoimmune Diseases and Biomarkers

2.1. Biomarkers in Myasthenia Gravis (MG)

Myasthenia gravis (MG) is predominantly caused by autoantibodies targeting postsynaptic nicotinic acetylcholine receptors (AChRs). These autoantibodies, responsible for muscle weakness and fatigue, have been neutralized using RNA aptamers. Specifically, RNA aptamers containing 2′-amino pyrimidines and 2′-fluoro pyrimidines have been shown to inhibit rat monoclonal antibodies (mAb198) specific to the immunogenic region of human AChRs. Both 2′-amino and 2′-fluoro RNA aptamers consisted of 89 nucleotides, with the latter exhibiting superior binding affinity. These findings suggest that a single aptamer may be derived from two distinct libraries via the systematic evolution of ligands by exponential

enrichment (SELEX). The aptamers demonstrated high serum stability, effectively inhibited antibody-AChR interactions, and neutralized autoantibodies from MG patients. Further studies revealed that RNA aptamers could inhibit both monoclonal antibodies targeting the immunogenic region on AChRs and patient autoantibodies modulating AChRs on human cells.

The chemical synthesis of aptamers has been enhanced by optimizing the structural attributes of these molecules. Secondary structure analysis, binding region evaluation, and site-directed mutagenesis were conducted on a 2′-fluoro-modified 89-nucleotide aptamer sequence. A shortened version, comprising 47 nucleotides, effectively protected cells from autoantibodies and demonstrated therapeutic potential for MG (Cho & Lee, 2009). These findings highlight the potential of RNA aptamers as a novel therapeutic strategy for MG.

2.2. Biomarkers in Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is the most prevalent autoimmune arthritis, affecting approximately 0.5–1.0% of adults worldwide. It is a chronic autoimmune condition of unknown origin, characterized by progressive inflammation, leading to severe joint pain, swelling, and stiffness in the limbs. Early detection of RA is crucial to prevent joint damage. Researchers have developed an electrochemical nanobiosensor to rapidly identify RA biomarkers, specifically anti-cyclic citrullinated peptide antibodies. This biosensor utilized molybdenum disulfide (MoS_2)-polyaniline (PANI) as the electrode's base matrix and a PANI-Au nanomatrix to detect biomarkers in human serum. Another study employed an amperometric biosensor using magnetic microbeads modified with biotinylated-anti-dsDNA to capture serum autoantibodies, enabling accurate detection in 100-fold diluted RA serum samples (Arévalo et al., 2020).

The earliest immunosensor for detecting CXCL7 chemokine and MMP3 metalloproteinase in RA employed screen-printed carbon electrodes with hydroquinone/hydrogen peroxide. It achieved detection limits of 0.8 ng mL^{-1} for CXCL7 and 1.2 pg mL^{-1} for MMP3. MicroRNAs (miRNAs), a class of short non-coding RNAs, play critical roles in cellular regulation. Optical sensors, particularly fiber optic sensors based on Lossy Mode Resonance (LMR), were used to detect the miRNA hsa-miR-223, a promising RA biomarker. Researchers also analyzed the expression profiles of circular RNAs (circRNAs) in peripheral blood mononuclear cells (PBMCs) of RA patients via RNA sequencing, revealing dysregulated circRNAs such as hsa_circ_0000396 and hsa_circ_0130438, which demonstrated potential diagnostic value (Yang et al., 2019). Similarly, circRNAs like hsa_circ_0044235 were found to be decreased in PBMCs, while hsa-miR-892a expression was elevated in RA patients (Luo et al., 2018).

An electrochemical immunosensor utilizing the avidin-biotin bio-recognition system and anti-cyclic citrullinated peptide antibodies was designed for RA diagnosis in human serum. Additionally, a peptide-based sensor validated by electrochemical impedance spectroscopy and ELISA confirmed the presence of RA autoantibodies. A dual electrochemical biosensor was also developed to detect rheumatoid factor and anti-cyclic citrullinated peptide autoantibodies simultaneously, achieving results in significantly less time than the ELISA method. To study synovial inflammation in RA, a three-dimensional synovium-on-a-chip was created, incorporating non-invasive optical light-scatter biosensing (Rothbauer et al., 2020).

RA is primarily marked by joint pain and deformity caused by chronic synovial inflammation, leading to joint destruction and disability. Biomarkers indicative of poor prognosis include high levels of acute-phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) tests. Additional non-specific biomarkers include tumor necrosis factor (TNF), interleukin-6 (IL-6), osteopontin, osteocalcin, amino-terminal telopeptide of type 1 collagen, carboxyl-terminal telopeptide of type 1 collagen, and matrix metalloproteinase-3 (Malek Mahdavi et al., 2022).

2.3. Biomarkers in Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a chronic and complex autoimmune disease with diverse clinical manifestations, causing considerable morbidity and mortality. It affects 40 to 50 individuals per 100,000, with a female-to-male prevalence ratio of 9:1. The identification of SLE-specific autoantibodies significantly facilitates diagnosis. Researchers have developed giant magnetoresistive (GMR) biosensor microarrays to detect interferon-associated autoantibodies alongside a chemokine score. Autoantigens such as histones H2A, H4, H2B, H3, Ribo P, dsDNA, U1-70K, Ro52, Ro60, La/SSB, and Smith have been analyzed using robotic contact microarrays for SLE diagnostic purposes. Additionally, human vascular cell adhesion molecule-1 has been introduced as a reliable urinary biomarker for SLE, assessed using non-redox electrochemical assay technology. An amperometric magnetic bead-based biosensor has also been employed to detect antibodies against aquaporin-4 in serum samples, offering cost-efficiency and point-of-care applicability for healthy individuals and patients with SLE and Alzheimer's disease (Arévalo et al., 2022).

Long noncoding RNAs (lncRNAs) have been implicated in SLE pathogenesis, notably by promoting the expression of complement factor H-related protein 5 and degrading miR-222. Considering the pivotal role of T cells in SLE etiology, researchers have investigated the regulatory mechanisms of circRNAs in the T cells of SLE patients. They identified a circRNA–miRNA–mRNA network involving eight circRNAs, four overlapping miRNAs, and 13 target mRNAs with regulatory roles in T cells. Moreover, miR-125a levels were found to be reduced in juvenile-onset SLE patients compared to controls, with increased plasma levels of IL-17 and IFN-γ in SLE patients, suggesting miR-125a as a potential therapeutic target for inflammation management in SLE (Eissa et al., 2021).

Studies have also linked interleukin-16 (IL-16) to SLE and RA pathogenesis, specifically evaluating the association between the rs1131445 polymorphism in the IL-16 gene and clinical characteristics in an Iranian population. Immunofluorescence tests remain a routine method for detecting anti-dsDNA (α-dsDNA) antibodies, a key serological marker in SLE blood samples. Recently, electrochemical biosensors have been employed for the rapid detection of α-dsDNA antibodies, facilitating autoimmune disease diagnosis and monitoring. Additionally, specific antibodies have been explored as potential treatments for various diseases. A novel Igβ and FcγRIIB cross-linking antibody, ASP2713, has been developed to bind B cells and induce negative feedback signaling, highlighting its therapeutic potential for SLE, where B cells contribute significantly to disease progression. Furthermore, the binding capabilities of a mouse anti-DNA IgG monoclonal antibody aptamer have been proposed for recognizing or neutralizing anti-DNA autoantibodies, benefiting SLE patients.

2.4. Biomarkers in Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS), characterized by progressive inflammation and neurodegeneration. This condition involves damage to oligodendrocytes and the myelin sheath caused by abnormal infiltration of immune cells, including T cells, B cells, and macrophages. The prevalence of MS is estimated at 30 cases per 100,000, with a female-to-male prevalence ratio of 3:1. Several studies have highlighted the role of microRNAs (miRNAs) as biomarkers in MS patients. For instance, levels of miR-21 and miR-146a/b in cell-free cerebrospinal fluid have been identified as potential biomarkers for active MS lesions. Another study examined the influence of B and T cells on miRNA expression regulation in MS patients. To detect miR-155 as a biomarker, researchers developed a biosensor incorporating carbon nanotubes and polypyrrole on a graphite sheet (Shariati et al., 2022).

A biosensing platform based on amperometry and carboxylated magnetic microparticles has been employed to detect anti-myelin basic protein autoantibodies, an essential biomarker in MS. This method demonstrated superior sensitivity, linearity, and shorter assay times compared to conventional ELISA kits (Guerrero et al., 2022). Elevated levels of anti-nuclear antibodies (ANA) have been observed in MS patients, similar to chronic viral hepatitis patients, including those with hepatitis C virus (HCV). Differentiating these conditions is possible through functional biosensors. Recent advancements include a lateral flow biosensor utilizing gold nanoparticles (RT-LAMP-AuNPs-LFB), offering a cost-effective, rapid, and sensitive detection method applicable in clinical settings. In this context, novel biosensor technologies could enhance clinical management for affected subgroups.

Additional research has demonstrated the potential of nanoparticle-based lateral flow biosensors with loop-mediated isothermal amplification for detecting hepatitis B antibodies in clinical saliva samples, showcasing high sensitivity. Techniques such as plasmonic-enhanced fluorescence sandwich immunoassays offer non-invasive, rapid, and specific biomolecule detection for systemic diseases (Riedel et al., 2017).

2.5. Biomarkers in Celiac Disease (CD)

Celiac disease (CD) is among the most prevalent autoimmune disorders, caused by the ingestion of wheat gluten and similar proteins found in barley and rye. This triggers an autoimmune response leading to small intestine atrophy and hyperplasia. CD is a chronic gluten-induced autoimmune disorder primarily affecting the intestinal lining in genetically predisposed individuals. Patients are advised to maintain a lifelong gluten-free diet. Diagnosing CD remains challenging due to its multifaceted clinical manifestations. Currently, CD diagnosis often relies on serological tests for serum antibodies such as anti-transglutaminase antibodies (anti-TGA). Blood tests for high concentrations of proteins, particularly anti-transglutaminase IgA (tTG) autoantibodies, exhibit significant sensitivity and specificity for CD diagnosis compared to antigliadin and antiendomysium assays. The superior diagnostic accuracy of blood tests for tTG antibodies was validated in previous studies, which highlighted their role in diagnosing and monitoring CD, though sensitivity and specificity remain a concern. Positive test results in CD patients were confirmed using the recombinant human tTG antibody method, which has been proposed for CD diagnostic screening.

Emerging biosensor-based technologies hold potential for clinical diagnostic applications by detecting serological biomarkers such as recombinant human tTG antibodies, particularly through electrochemical immunosensors. These tools are effective in determining positive and negative CD serum samples, offering a non-invasive, sensitive, selective, and stable biomarker detection method for CD diagnosis (Pasinszki & Krebsz, 2018). Analytical techniques, such as immunosensors based on nanoelectrode arrays, have recently been explored. Researchers have developed portable devices that generate electrochemical signals processed through integrated IoT-WiFi boards, enabling cloud-based result sharing for physicians or caregivers. These electrochemical platforms utilize screen-printed electrodes functionalized with gold nanoparticles (AuNPs) and immobilized transglutaminase to capture anti-TGA antibodies. The detection system generates amperometric signals via a secondary antibody labeled with alkaline phosphatase (AP) (Giannetto et al., 2018).

Biosensors have demonstrated significant promise in biomarker detection, where the electrode materials and architecture are pivotal in achieving rapid and sensitive outcomes. Researchers identified three circulating miRNAs—miR-192-5p, miR-215-5p, and miR-125b-5p—as non-invasive biomarkers for diagnosing CD in pediatric patients with low TGA-IgA titers who adhere to a gluten-free diet. Furthermore, a nanostructured electrochemical immunosensor was designed to detect IgA isotypes of anti-tissue transglutaminase, offering a low detection limit for human serum samples from celiac patients. Since the precise etiology of CD is unclear, recent investigations have examined the roles of various genes and miRNAs

in CD patients. A study in pediatric CD patients showed increased expression of miRNA-21 and decreased expression of miRNA-31 in serum, demonstrating their potential as non-invasive biomarkers. Moreover, the expression levels of inflammation-related miRNAs, including miRNA-146a, miRNA-155, miRNA-21, and miRNA-125b, were elevated in peripheral blood, implicating these miRNAs in immune processes and suggesting their utility as diagnostic biomarkers for CD (Bascuñán et al., 2020).

2.6. Biomarkers in Behcet's Disease (BD)

Behcet's disease (BD) is a chronic, relapsing systemic vasculitis of unknown etiology, characterized by clinical manifestations that include mucocutaneous symptoms and cardiac involvement (Alpsoy et al., 2021). BD, along with related conditions such as Sweet syndrome, is defined as a multisystem inflammatory disorder. Advances in microfluidic, microelectronic, and electrochemical measurement technologies have facilitated the development of potential biosensors for healthcare monitoring. Sweat components have been identified as promising biomarkers for non-invasive health monitoring. In a related application, researchers evaluated vascular endothelial growth factor (VEGF) in clinical tears to detect and monitor diabetic retinopathy using an electrochemical reusable aptasensor. This platform utilized a hybridization chain reaction, CeO_2 nanoparticles, and strand displacement reaction, demonstrating potential for non-invasive diabetic retinopathy screening via clinical tear samples (Mei et al., 2021).

Studies have reported significantly higher serum microRNA-146a expression in Egyptian BD patients compared to controls (Ibrahim et al., 2019). Additionally, BD patients exhibited increased Th17 cells and Th17-associated cytokines, alongside reduced regulatory T cells (Treg), IL-10 levels, and forkhead box P3 mRNA expression (Ahmadi et al., 2019). Recent findings also indicate that miRNA-499 expression and IL-17 levels were markedly elevated in BD patients relative to healthy controls. Further research has identified several miRNAs with differential expression in BD patients, including upregulated miRNAs such as miR-20a, miR-34a, miR-197, U6snRNA, miR-205, miR-222, miR-296, miR-302a, miR-302c, and miR-372, and downregulated miRNAs such as miR-518b and miR-874 (Eyerci et al., 2020).

The evaluation of immune cell profiles and miRNA expression patterns presents opportunities for prognostic biomarker development and therapeutic strategies in BD patients.

3. Application of Biosensors in Autoimmune Diseases (ADs)

3.1 DNA-Based Biosensors

Cell-based biosensors utilize genetically modified living cells to detect specific biomarkers. Researchers have developed a CHO-K1 cell line capable of expressing both a chimeric thyroid-stimulating hormone receptor (TSHR-Mc4) and a luciferase-based cAMP biosensor, which effectively detects anti-TSHR autoantibodies in Graves' disease. Despite advancements, there are challenges that hinder broader applications of cell-based biosensors. DNA-based electrochemical biosensors (E-DNA) rely on DNA oligomers covalently attached to an electrode surface. These oligomers undergo conformational changes depending on whether the target is bound or unbound. By linking a redox-active molecule, such as methylene blue, to the oligomer, the conformational alteration modifies electron transfer kinetics at the electrode surface, resulting in a measurable current change. An E-DNA biosensor was designed and tested to detect Celiac disease (CD) autoantibodies. This mechanism involves binding CD-specific autoantibodies to a synthetic epitope, inducing a conformational change and altering the environment of a fixed redox reporter, which reduces the measurable current (Nguyen et al., 2021).

DNA sensors, which are DNA-binding proteins, act as components of the innate immune system to detect DNA damage and disruptions in cellular homeostasis. These sensors activate intracellular signaling cascades as part of the immune response. This mechanism is

critical during viral infections, as the production of interferons (IFNs) provides robust immunity by inhibiting viral replication and preventing viral spread to neighboring cells. DNA sensors not only promote the generation of type I IFNs but also initiate programmed cell death as part of the host's immune defense. Effective immune responses require the host to differentiate between viral and self-DNA, which is influenced by various factors, including (a) the length and 3D structure of cytotoxic DNA molecules, (b) subcellular localization, (c) DNA methylation status, and (d) the association of chromatin-binding proteins with cytotoxic DNA (Andreeva et al., 2017).

Innate immune DNA sensors are categorized into two groups based on their localization and expression. The first group comprises endosomal DNA sensors, such as Toll-like receptor (TLR) family members, which are situated on the endosomal membranes of immune cells like macrophages, dendritic cells (DCs), and B cells. These sensors detect cytotoxic DNA from bacteria or viruses within lysosomes and endosomes. The second group includes cytosolic DNA sensors capable of recognizing nucleic acids in the cytoplasm across various cell types.

3.2 Peptide-Based Biosensors

Peptides exhibit remarkable versatility due to their ability to self-assemble into ordered 1D, 2D, and 3D structures, making them useful for designing flexible scaffolds. Their adaptability in modifying secondary structures by altering amino acid sequences or optimizing interactions between adjacent peptides allows peptides to function as bioreceptors (recognition units). Peptides are easily synthesized through rapid and cost-effective techniques and exhibit excellent biocompatibility, chemical stability, structural integrity, and fast response times in electrochemical detection. These properties make peptide-based biosensors ideal for bioassays and pave the way for sophisticated biomolecular systems and challenging analyses. Using these biomolecules offers novel diagnostic and therapeutic options for autoimmune diseases. Autoantibodies and specific biomolecules associated with various systemic autoimmune diseases can aid in developing diverse biosensor types.

An epitope vaccine candidate was designed using B- and T-cell epitopes to act as an immunogen and elicit an immune response in the host system. Immunosorbent biosensor assays offer a cost-effective and user-friendly alternative to traditional ELISA tests. Following partial stabilization achieved through vaccines, additional research is required to address future control measures for epidemics, including autoimmune diseases. Advanced vaccine designs, such as multi-epitope vaccines combined with nanobiosensor array chips, have shown promise in enhancing protein domain sensitivity. By integrating anti-human IgG on nanobiosensor chip surfaces, multi-epitope vaccines are recognized more effectively and rapidly by the immune system. This innovation enables large-scale and rapid evaluation of vaccine efficacy. Recent developments include the nanoplasmonic immunosorbent assay platform, a high-throughput tool for assessing vaccine effectiveness (Vogel et al., 2022).

Biomarkers offer a valuable approach for identifying, classifying, and treating autoimmune disease patients. Autoantibodies with varying specificities have been identified in ADs, with some being disease-specific and others associated with multiple diseases. These attributes make autoantibodies useful as diagnostic biomarkers (Zhao, 2020). Since autoantibodies serve as diagnostic markers, biosensors are often designed based on antigen–antibody interactions. Biosensor transducers can be optical, magnetic, mechanical, or electrochemical. This study highlights the potential of biosensor technology, particularly electrochemical biosensors, for developing affordable and accessible diagnostic tools and products for monitoring disease progression and treatment responses in ADs.

Conclusion and Future Perspectives

Autoimmune diseases (ADs) result from the immune system erroneously targeting the body's tissues, producing inflammatory molecules and autoantibodies. ADs are thought to arise from an interplay of genetic and environmental factors. Environmental influences, such as ultraviolet radiation, chemical exposure, and infectious agents, may expose self-tissue antigens in susceptible individuals, triggering autoimmune responses. This leads to the production of numerous cytokines and autoantibodies, which cause tissue damage. Currently, ADs are diagnosed after symptoms manifest, and treatment strategies focus on symptom management rather than cure.

Biosensors offer an advanced approach for precise disease monitoring and assessing drug efficacy in clinical trials. Biomarkers play a critical role in signaling pathogen-induced inflammation and the progression of ADs. Conventional AD diagnostic methods rely heavily on physician assessment and basic laboratory tests, which often lack sensitivity for detecting early molecular changes. Consequently, AD diagnosis frequently occurs too late to prevent tissue damage.

Although biosensors hold great promise, challenges remain, including complex manufacturing processes, high costs, limitations in analyzing real samples, and measurement errors. Future advancements must simplify production, enhance cost-effectiveness, enable multiplex detection, and expand applicability to real-world samples. Biotechnological advancements over the past decades have facilitated the discovery of new biomarkers and innovative strategies for designing biosensors. This review examined the progress in biosensor-based approaches for monitoring biomarkers in ADs. The integration of biosensor technology could revolutionize the identification of specific biomolecules for diagnosing ADs, enabling targeted therapies and tracking drug response effectively.

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