The Potential Role of Mass Spectrometry in the Diagnosis of Immune-Related Diseases

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Abstract: Mass spectrometry (MS) has emerged as a powerful analytical technique with significant potential for advancing the diagnosis of immune-related diseases. This comprehensive review examines the fundamental principles of MS technology and its diverse applications in autoimmune disorders, neuroimmune conditions, and cancer-related immune diseases. Through detailed analysis of recent research, we demonstrate how MS-based approaches enable precise characterization of autoimmune antibodies, identification of novel biomarkers, and insights into disease mechanisms. The exceptional sensitivity and specificity of MS techniques facilitate detection of low-abundance proteins, post-translational modifications, and complex immune signatures that traditional methods often miss.

Keywords: Mass spectrometry;Immune-Related diseases;Biomarkers;Diagnosis; Proteomics

1.Introduction

The diagnosis of immune-related diseases presents considerable challenges in clinical practice due to their complex pathogenesis, heterogeneous clinical presentations, and frequently overlapping disease manifestations.Mass spectrometry has evolved from primarily a basic research tool to an increasingly indispensable technology in clinical diagnostics. Its exceptional analytical capabilities allow for the simultaneous detection and quantification of thousands of proteins, peptides, and metabolites from minimal sample volumes. In the context of immune-related diseases, MS facilitates the identification of disease-specific biomarkers, characterization of post-translational modifications that generate autoantigens, and comprehensive profiling of immune cell populations . This review aims to provide a comprehensive overview of the current applications and future potential of MS technology in diagnosing various immune-related disorders, focusing on its implementation in autoimmune diseases, neuroimmune conditions, and cancer-related immune pathologies. Additionally, we discuss current limitations and emerging trends that are shaping the future of MS-based immune disease diagnostics.

2.Fundamentals and Classification of Mass Spectrometry Technology

2.1 Basic Principles of Mass Spectrometry

Mass spectrometry operates through a fundamental process that involves ionizing chemical compounds to generate charged molecules or molecular fragments, followed by measuring their mass-to-charge ratios. This analytical technique comprises three essential components: an ion source, a mass analyzer, and a detector. The ion source converts analyte molecules into gas-phase ions; the mass analyzer separates these ions based on their mass-to-charge ratios (m/z); and the detector records the number of ions at each m/z value. In biological applications, the two most prevalent ionization techniques are electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI), both of which enable the soft ionization of large biomolecules without significant fragmentation[1].

2.2 Classification of MS-Based Approaches in Biomedical Applications

In the context of immune disease research and diagnostics, MS-based approaches can be broadly categorized into several types based on their analytical focus and methodology. Bottom-up proteomics, also known as shotgun proteomics, involves digesting proteins into peptides followed by LC-MS/MS analysis and has become the most widely employed approach for large-scale protein identification and quantification from complex biological samples . This method offers high proteome coverage and is particularly valuable for biomarker discovery from various clinical specimens, including plasma, urine, tissue, and cerebrospinal fluid.

Another significant category includes techniques focused on post-translational modification (PTM) analysis, which is particularly relevant to autoimmune diseases where modifications such as citrullination significantly alter protein immunogenicity. MS enables comprehensive profiling of various PTMs, providing insights into disease mechanisms and potential diagnostic biomarkers . Additionally, mass cytometry (CyTOF) combines flow cytometry with MS by using metal-tagged antibodies instead of fluorophores, allowing for high-dimensional single-cell analysis of over 40 parameters simultaneously. This technology is especially powerful for characterizing immune cell populations and their functional states in various immune-related conditions[2].

3 MS Applications in Autoimmune Disease Diagnosis

3.1 Rheumatoid Arthritis and Psoriasis

Mass spectrometry has demonstrated remarkable utility in advancing the diagnosis and understanding of rheumatoid arthritis (RA), particularly through the characterization of anti-citrullinated protein antibodies (ACPAs) that serve as specific serological markers for this condition. Research has employed MS-based approaches to identify citrullinated peptides within serum immune complexes and synovial tissue antigens, revealing distinct protein profiles between ACPA-positive and ACPA-negative RA patients . These findings not only enhance our comprehension of RA pathogenesis but also suggest potential diagnostic biomarkers for ACPA-negative patients who pose diagnostic challenges in clinical practice.

In psoriasis, another prevalent autoimmune disorder, MS technology has been successfully implemented to establish innovative methods for serum immune complex (IC) identification. One study developed an MS-based technique that identified 360 autoantigens in pooled serum samples from psoriasis patients, representing an eight-fold increase compared to previous methodologies . This substantial expansion of the psoriasis autoantigen repertoire provides unprecedented opportunities for understanding disease mechanisms and developing novel diagnostic approaches. The MS-based platform for immune complex analysis enables comprehensive antigen profiling, facilitating the identification of disease-specific autoantigens that may serve as biomarkers for diagnosis, disease monitoring, and treatment response assessment[3].

3.2 Autoimmune Pancreatitis and Kidney Diseases

Autoimmune pancreatitis (AIP) represents another area where MS applications show significant diagnostic potential. Studies have focused on analyzing immunoglobulin Fc glycosylation patterns using liquid chromatography-tandem mass spectrometry (LC-MS/MS), revealing distinctive glycosylation profiles associated with type 1 AIP . These glycosylation signatures not only contribute to disease pathogenesis but also offer potential as diagnostic biomarkers and indicators of treatment response. MS-based monitoring of therapeutic monoclonal antibodies like rituximab (used for recurrent type 1 AIP) concurrently with endogenous antibody features enables comprehensive treatment assessment and personalized management strategies[3].

4 MS in Neuroimmune and Demyelinating Disorders

4.1 Biomarker Discovery for Demyelinating Diseases

Mass spectrometry has made significant contributions to the understanding and diagnosis of immune-mediated demyelinating diseases through comprehensive cerebrospinal fluid (CSF) and serum proteomic analyses. A compelling application of this technology is evident in a study that utilized tandem mass tag (TMT) labeling combined with LC-MS/MS to identify potential biomarkers for diagnosing and differentiating demyelinating disorders . The investigation revealed 101 differentially expressed proteins between demyelinating disease patients and controls with non-inflammatory neurological diseases, along with 45 differentially expressed proteins between Guillain-Barré syndrome (GBS) and multiple sclerosis (MS) subgroups. These protein signatures offer valuable insights into disease mechanisms and potential diagnostic applications.

Bioinformatic analysis of the MS-derived data identified significant enrichment in lipid metabolism pathways, including cholesterol metabolism, phosphatidylinositol 3-kinase-protein kinase B signaling pathway, and complement and coagulation cascades . Subsequent validation studies demonstrated that conventional lipid parameters—including triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1, and apolipoprotein B—showed significant differences between demyelinating disease patients and healthy controls, as well as between GBS and MS patients. These findings suggest that lipid-related biomarkers may assist in the diagnosis and differential diagnosis of immune-mediated demyelinating diseases, highlighting the potential of MS-based approaches to uncover clinically useful biomarkers.

4.2 Monitoring Immunotherapy-Related Neurotoxicity

As cancer immunotherapies, particularly immune checkpoint inhibitors (ICIs), become increasingly prevalent, the management of immune-related adverse events (irAEs) has emerged as a significant clinical challenge. Mass cytometry (CyTOF) has proven valuable in characterizing the immune cell signatures associated with neurological irAEs (irAE-n). One comprehensive study employed CyTOF to analyze peripheral blood samples from 34 irAE-n patients and 49 control patients without irAE-n, assessing 48 protein targets to identify specific immune cell populations associated with neurotoxicity .

5 Emerging Applications in Cancer Immunotherapy

5.1 Characterizing the Tumor Immune Microenvironment

Mass spectrometry has become an indispensable tool for characterizing the tumor immune microenvironment, providing critical insights into cancer-immune interactions and potential therapeutic targets. Imaging mass cytometry, an advanced MS-based technology, enables simultaneous detection of over 40 markers on tissue sections while preserving spatial information . This powerful approach allows researchers to investigate immune cell infiltration, spatial relationships between different cell populations, and functional states of immune cells within the tumor microenvironment. The preservation of architectural context is particularly valuable for understanding immune evasion mechanisms and developing strategies to overcome them.

The Hyperion XTi mass cytometry system exemplifies how MS technology advances tumor immunology research by combining laser ablation with inductively coupled plasma MS to enable highly multiplexed tissue imaging . This system and similar platforms facilitate comprehensive analysis of the tumor immune microenvironment, contributing to our understanding of disease mechanisms, drug resistance, and novel drug target development. The information gained from these MS-based applications has significant implications for cancer diagnosis, prognosis assessment, and treatment selection, moving us closer to personalized cancer immunotherapy.

5.2 Immunopeptidomics and Vaccine Development

Immunopeptidomics, the large-scale study of peptide antigens presented by major histocompatibility complex (MHC) molecules, represents another promising application of MS technology in cancer immunology. Through immunopeptidome analysis, researchers can identify tumor-specific antigens that can be targeted by immunotherapeutic approaches or incorporated into cancer vaccines.

In the context of infectious disease vaccines, MS has been employed to characterize antibody responses following COVID-19 vaccination. Research analyzing immunoglobulin Fc glycosylation patterns in dialysis patients who received SARS-CoV-2 vaccines revealed distinctive glycosylation features, including increased afucosylation of total IgG following vaccination and infection, as well as regulated galactosylation profiles associated with immune regulation.For antigen-specific antibodies, researchers observed decreased IgG bisection and increased IgG sialylation, with significant alterations across most IgG, IgA, and IgM glycans.

5.Conclusion

Mass spectrometry has emerged as a transformative technology with substantial potential to advance the diagnosis and management of immune-related diseases. Its unparalleled analytical capabilities enable comprehensive characterization of immune complexes, autoantibodies, cellular populations, and signaling molecules that underlie disease pathogenesis. While challenges related to standardization, complexity, and cost remain, ongoing technological advancements and methodological refinements are steadily addressing these limitations. The integration of MS with other omics technologies and artificial intelligence promises to further enhance its diagnostic utility, paving the way for personalized approaches to immune disease management.

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