



OMICS Approaches to Understand Etiology of Multiple Sclerosis; A Literature Review

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ABSTRACT

Multiple Sclerosis (MS) is a central nervous system (CNS) disorder with underlying autoimmune mechanisms, marked by immune-mediated destruction of the myelin sheath of axons. MS has a complex genetic, metabolic, and immune etiology and pathophysiology, which imposes challenges for successful treatment strategies. The present document discusses the genetic and environmental risk factors of the demyelinating disease and illustrates the OMICS approaches for a deeper understanding of the etiology of MS. The application of OMICS approaches provides information about the different biomarkers associated with MS and forms the basis for prognostic, diagnostic, and therapeutic tools.

1. INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune central nervous system (CNS) disorder that demonstrates neurological, cognitive, and physical complications. [1] MS is a prevalent demyelinating disorder affecting over 2.8 million individuals globally. [2] This disease is characterized by focal infiltration of macrophages and T lymphocytes, comprising multifocal zones of inflammation in the CNS. Inflammation and destruction of the myelin sheath lead to the development of CNS plaques. The CNS plaques are composed of inflammatory cells, products of inflammation, astrogliosis, and transected and demyelinated axons. The inflammatory lesions may cause neuronal dysfunction, including visual disturbances, fatigue, sensorimotor defects, autonomic defects, ataxia and emotional disturbance. [3-5] The onset of MS has a multifactorial course, including genetic and environmental factors. [6]

The pathogenesis of MS involves acquired dysregulation and aberrant activation of the immune system, which gives rise to inflammatory processes that contribute to demyelination and damage of the axons in the CNS. [7] Environmental factors include infections, geographical attributes, seasonal influences, dietary factors, the composition of the gut microbiome, and environmental toxins that may exacerbate the onset of MS. [8, 9] The association of certain racial and ethnic groups with the incidence of MS indicates the genetic basis of the onset of MS. [10] In contrast to the Asian and Hispanic population, African American and Caucasian populations are at an increased risk for developing MS. [11] Although the etiologic mechanisms of MS are unclear, up to 200 genes are associated with an increased risk for MS, with the highest evidence available for human leukocyte antigen (HLA)-DRB1. [12, 13].

Inflammatory cells invading myelin-reacting T cells, B cells or plasma cells, macrophages, and dendritic cells release inflammatory cytokines, chemokines, and antibodies in these lesions, according to histopathology. [14] As a result, the research has agreed that T lymphocytes are the primary drivers of this disease, with B lymphocytes and naïve immune cells also playing a role. [15, 16] In addition, indigenous CNS cells such as astrocytes have a role in disease pathogenesis by maintaining a pro-inflammatory environment. Myelin breakdown and neuronal loss are caused by isolated regions of inflammation in the CNS, which present clinically in people as numbing, exhaustion, high sensory disturbances, and disability.[17].

For identifying and assessing MS, physicians mostly use inductive and deductive methodologies; nevertheless, Magnetic resonance imaging, clinical symptoms, or other evaluations cannot perfectly characterize action, progress, required steps, and MS relapse. Many alternative methods have been explored to examine the diverse biological mechanisms and altered biomarkers throughout MS to acquire a greater understanding of biomarkers, a trait that may be tested and assessed scientifically as a sign of a basic biological function, a pathological process, or pharmacological reactions to a clinical treatment [18].

To find relevant biomarkers, researchers often utilize 2 methods: hypothesis-based and discovery-based methodologies. The hypothesis-based analysis concentrates on figuring out how diseases work. The discovery-based biomarkers approach tries to determine a shift in concentrations of certain components such as enzymes and proteins. [19] However, the intricate processes and etio-pathology of MS make it challenging to find viable markers for diagnostic and prognostic predictions. Researchers are addressing the development of a novel and suitable biomarker by introducing new technologies such as genomics, transcriptomics, epigenetics, proteomics, and metabolomics, which would provide maximum throughput of details relating to disease etiology [20].

Comprehensive omics analyses are carried out in the first step to find interesting target compounds. Omics studies give enormous statistical information regarding prevalent chemicals within every type or phase of MS, possibly correlating

with pathogenicity, intensity, and pathogenesis. [21] Researchers can use these databases to look for new and effective MS biomarkers.

Amidst these advancements, the intricacy of MS poses a barrier to predictive and therapeutic biomarkers.[22] Particular and credible biomarkers that assist in understanding underlying pathways and etiopathogenesis of MS are desperately needed. These biomarkers might be used in all phases of clinical outcomes to detect MS, anticipate improved clinical outcomes, eliminate unwanted investigations, as well as mentor further management.[19] With a rise in the application of OMICS approaches to understanding signaling pathways for both normal and disease states. OMICS approaches encompass genomics, miRNAomics, proteomics, transcriptomics, and metabolomics. [23] Adequate understanding of the etiologic mechanisms of MS is crucial to the development of effective preventive and treatment approaches for MS. This literature will concentrate on the possible impact of OMICS approaches in MS, from biomarker creation to personalized medicine. This review summarizes the OMICS approaches for the etiologic understanding of MS.

2. LITERATURE REVIEW

2.1. Omics Approaches

For the last two decades, "OMICS" processes have started to emerge as a favorable method for identifying biological mechanisms and differentiating upregulated molecules, unbiased of a variety of disease-causing agents. Proteomics can thus be used to explore biomarkers, promising therapeutic benchmarks, and novel adapting processes. [24] Although all medicinal techniques are based on the disorder's inflammation perspective, a remarkable amount of omics studies have been performed on experimental model specimens and sick people with Multiple Sclerosis to date [25].

Furthermore, there has been a surge in research into the relationship between both genome and phenotype in cells or organisms. Even a comprehensive knowledge of the genome's position and proteome in a biological body doesn't represent its phenotype, according to new research. As a result, concerning the proteome, metabolomics research is critical; as a result, metabolomics is now widely used as a standalone strategy. [26] Metabolomics and proteomics

collectively provide an unbiased array of techniques for investigating pathophysiologic mechanisms [27]. The integration of proteomics and metabolomics yields precise elucidation of disease mechanisms and identification of therapeutic targets, as evidenced by studies focusing on kidney disease, cardiovascular research, and neurodegenerative diseases. [27-29] The role of epigenetics in MS etiology, as well as other inflammatory illnesses, has gained significant attention in past years. Epigenetics, which encompasses medications that can modify changeable and dynamic epigenetic traits, has also been recognized as a possible medicinal strategy to treat MS [30].

2.2. Metabolomics in MS

While the etiologic mechanisms of MS remain unclear, metabolic disruption induces alterations in the metabolome which include changes in the metabolic pathways and the derived metabolic products.[31] The measurement and analysis of metabolites in different biological samples form the cornerstone for identifying the differences between pathological and non-pathological mechanisms. Two approaches to metabolite measurement include targeted validation-tandem and untargeted-discovery-global. The targeted approach is employed for validating the metabolites, which are identified using the untargeted approach. The untargeted approach generates a hypothesis for the detection of all the metabolites, however, the targeted analysis identifies a maximum of 20 metabolites only. Both the targeted and untargeted approaches are adapted for precision in the identification and quantification of metabolites [32].

Cerebrospinal fluid (CSF)-based metabolic profiling is an important metabolomic approach for assessing the pathophysiologic mechanisms of MS. To date, various metabolomic experiments have been conducted to evaluate the metabolic profiles of individuals suffering from MS as compared to healthy individuals. Altered energy metabolism in MS is associated with greater levels of fructose and lactate in the CSF. In contrast to healthy individuals, individuals with MS have lower levels of phenylalanine and creatinine in the CSF. Cohort studies identify the differences in the levels of metabolites in active and inactive disease states. The analysis of the CSF metabolome reveals an association between the inflammatory activity

of MS plaque in the CNS with defects in the metabolism of organic acids in the CNS including lactate. Mitochondrial dysfunction in MS, in addition to alterations in energy metabolism, leads to an increase in the levels of lactate, sorbitol, and fructose in the CNS. These metabolites are also associated with neurological disabilities in individuals with MS. Mitochondrial dysfunction in MS is related to the onset of extra-mitochondrial metabolism of glucose.

A distinct lipidomic signature is associated with the onset and progression of MS. Disruption in the synthesis of fatty acids is associated with a decline in the levels of acetyl CoA in the CNS [33].

Despite its promise, the application of metabolomics in clinical settings faces several challenges. Variability in study designs, sample handling, and analytical techniques can lead to inconsistent results across different studies. Moreover, the heterogeneity of MS itself complicates the identification of universal biomarkers applicable to all patients [33, 34].

2.3. Genomics in MS

Genome-wide association studies (GWAS) using NGS have identified numerous genetic variants associated with MS susceptibility. These studies have implicated genes involved in immune function, such as HLA-DRB1, as well as novel loci, providing insights into the genetic architecture of MS. [35] The International MS Genetics Consortium has identified up to 200 genes associated with a greater risk for the onset of MS. [36] The best candidate genes include the major histocompatibility complex (MHC) region. [37] In individuals with MS, the major immune cell types comprise MS susceptibility genes with the risk variants concentrated in the brain's resident immune cells. Genomic approaches for identifying the etiologic basis of MS play an important role in assessing the heritability and development of this demyelinating disease. The enrichment of susceptible genes in the resident immune cells of the CNS explains the activation of autoimmune processes in the CNS, however, altered peripheral immune responses are also associated with the onset of MS. [36].

The HLA gene cluster, situated within the polymorphic MHC region on chromosome 6p21,

encodes receptors that play a crucial role in the recognition of antigens, both self and foreign.[38] This gene cluster is also implicated in the regulation of autoimmune diseases, particularly MS. GWAS have successfully identified non-HLA gene loci associated with MS, including the interleukin-2 receptor alpha (IL2RA) locus located on chromosome 10p15. The IL2RA gene, also referred to as CD25, encodes the alpha chain of the IL-2 receptor. Daclizumab, which was previously administered to MS patients, specifically targets the alpha chain of the IL-2 receptor. Furthermore, the association of MS with the X chromosome elucidates the observed increased incidence of the disease in females compared to their male counterparts [39].

2.4. Proteomics in MS

In contrast to genes, the proteomes are dynamic entities and are subject to changes in response to environmental and physiological alterations. The proteome profiles in individuals suffering from MS comprise consistent changes in the quantities of structural, blood-related, immune-competent, and metabolic proteins. Serum or blood samples are frequently used for proteomic analyses; however, urine, saliva, and tears are not routinely used for the assessment of proteomes in the body. [40]

The elevation of the levels of serum neurofilament light chain is an important biomarker for MS and degenerative disorders, the same protein can be elevated in MS patients with an altered renal function. During the proteome analysis, the cerebral tissue is given priority, however, splenic tissue and mononuclear cells in the blood are also assessed for the protein biomarkers of MS. The proteome assessments utilize the spinal cord tissue, owing to its predominant involvement in MS. The analysis of CSF for protein biomarkers tends to be more informative than the analysis performed using the blood samples of MS patients. This is due to two reasons – first, the protein biomarkers are localized to the CNS and found in lesser amounts in other regions of the body; secondly, the drainage of proteins indicates the pathological status of the CNS. However, the collection of CSF samples for proteomic analysis requires trained personnel and specialized equipment. The abundant protein species in the CSF sample of MS patients include carbonic anhydrase I, hemoglobin, catalase, and

peroxiredoxin [41].

Studies also identified the altered expression of heat shock proteins (HSP) in the body fluid samples of MS patients. The heat shock proteins protect the cells against environmental stressors and mediate the protein folding, intracellular signaling, and regulation of the cell cycle. Alpha-crystallin B chain (CRYAB) is a small heat shock protein that has an altered level of expression in MS patients. In the CNS, this heat shock protein plays a pivotal role in the protection of astrocytes and oligodendrocytes against apoptosis. CRYAB performs this function by suppressing the activity of caspase. CRYAB also inhibits the neuroinflammatory signaling pathways [24, 42].

Despite these advancements, challenges remain in standardizing proteomic methodologies and ensuring robust validation of identified biomarkers. Inconsistencies in analytical techniques can lead to contradictory results across studies, highlighting the need for consensus on methodological approaches.

2.5. Transcriptome in MS

Transcriptome refers to transcripts in the cells concerning physiological conditions and different developmental stages. The transcriptome determines the functional aspects of the genome and is important for the understanding of developmental stages and disease processes. [43] Stress- and inflammation-related changes in gene expression patterns in CNS macrophages are evident in individuals suffering from MS. The altered transcriptomic profile of macrophages is consistent with the demyelination and remyelination of the axons in the CNS. Transcriptomic profiling offers early diagnostic opportunities for MS. [44, 45].

2.6. Micro RNAomics in MS

Dysregulation of microRNAs in MS forms the basis of the diagnostic and prognostic importance of microRNAs. MiRNA-34a, miRNA-326, and miRNA-155 are in abundance in the active lesions in MS in addition to other miRNAs.[46] These miRNAs modulate the differentiation of Th17 cells which are involved in the inflammatory pathways in MS. [47].

2.7. Machine Learning Model for OMICS Approaches

Machine learning models, along with data mining tools, are integral to discovering, analyzing, and interpreting biomarkers using the OMICS approaches. This facilitates the identification of

molecular mechanisms underlying a certain pathological process such as MS. Different machine learning models analyze data obtained from the application of OMICS approaches to identify the molecular biomarkers, which then form the basis for the diagnosis and treatment of diseases. [48]

The integration of machine learning and OMICS approaches in identifying biomarkers and formulating diagnostic and treatment strategies is associated with multiple challenges. The gathered data is often heterogeneous; for instance, data regarding proteomics and transcriptomics has different scaling techniques and data distribution; therefore, it is challenging to analyze the sparse data. [48] Moreover, specific pathologies have diverse characteristics that often outnumber the given classes in the machine learning software. There may be an imbalance between the given classes and the pathology features under consideration. Machine learning for analyzing and interpreting data gathered using OMICS approaches is accompanied by higher costs and increased demand for storage space. It is important to choose an appropriate and relevant machine learning algorithm to apply to the given data and obtain correct information about the biomarkers and their association with the given pathology. [49] Support vector machine (SVM) is an important machine learning method used in conjunction with genetic analysis for MS. The SVM model identifies a discriminant function such as a hyperplane to classify the data set obtained by the application of OMICS approaches in MS patients. This discriminant function classifies the data set on either side of the hyperplane and maximizes the hyperplane. Kernel function is applied to non-linearly separable data for its transformation into higher dimension, followed by the identification of decision boundaries. Other machine learning methods relevant to the genetic analysis in MS patients include random forest and naïve bayes classifier [50].

2.8. Epigenetics Approach In MS

The specific cause of this neurodegenerative condition is unknown, but numerous genetic and environmental risk factors appear to be implicated. [51].

Vitamin D status, Epstein Barr virus infection, and smoking are all potential environmental risk factors in MS, which can confirm the significance of epigenetics in MS. [30, 52] Epigenetics, in reality,

serves as a link between environmental influences and a person's genetic makeup. Epigenetic pathways significantly influence remyelination and the pro-inflammatory response in MS. Key mechanisms include the regulation of BDNF by MeCP2, modulation of neuroimmune responses by GAA, enhancement of the ISR, and the role of cholesterol homeostasis in oligodendrocytes. [53] Additionally, TREM2 activation on microglia, the interplay between WNT/ β -catenin and PPAR γ pathways, and the polarization of M2 microglia and macrophages are crucial for promoting remyelination and reducing inflammation. [54] Each of these epigenetic variables linked to MS can be exploited as a diagnostic for early detection and more effective treatment options

There is accumulating evidence that vitamin D exerts effects on epigenetic factors. The vitamin D receptor (VDR) engages with chromatin modifiers and remodelers, which may modulate epigenetic processes. This relationship is further substantiated by the regulation of these chromatin modifiers and remodelers, as well as the impact of the VDR and its ligand on DNA methylation. [55, 56].

Studies have reported that in particular group of individuals smokers have a 40 percent to 80 percent higher risk of MS than non-smokers, according to epidemiological research. [57, 58] The impact of cigarette smoke on epigenetic variables such as DNA methylation, histone acetylation, and miRNA expression has been studied extensively. [55] The impact of cigarette smoke on DNA methylation, for example, has been shown. [59].

2.9. Long Non-Coding RNA Biomarkers in MS

Long non-coding RNAs (lncRNAs) are nonprotein coding transcripts that are longer than 200 nucleotides in length. The manner of action of these compounds is quite remarkable. Unlike conventional RNAs, which migrate away from the transcriptional site as they are created, these lncRNAs remain put. They are transcribed either in antisense or overlapping orientations relative to protein-coding genes (long intergenic/intervening ncRNAs) or from intergenic regions (long intergenic/intervening ncRNAs) [60].

In autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and psoriasis, as well as numerous multigenic human

diseases, LncRNA may play a key role. The relative link between various types of lncRNA and MS patients is poorly understood [61].

3. DISCUSSION

The review article consists of information related to different OMICS approaches to understanding the etiology of MS, with a subsequent understanding of the diagnostic, prognostic, therapeutic, and preventive characteristics of the demyelinating disease. OMICS approaches emphasize the role of molecular entities in the onset of MS. The approaches include genomics, miRNAomics, proteomics, transcriptomics, and metabolomics. OMICS approaches function as powerful tools for identifying and analyzing the pathophysiology of MS as well as devising diagnostic and treatment strategies for this disease.

In addition to MS, OMICS approaches have been adapted for identifying the biomarkers of different inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease. Identification of the predictive biomarkers allows for a thorough understanding of the etiological mechanisms and identification of optimal therapeutic strategies. The assessment of the biomarkers also eliminates the need for unnecessary investigative and diagnostic procedures including lab evaluations and radiologic imaging. [62]

A longitudinal cohort study of a total of 49 participants with MS using OMICS approaches to identify altered interactions of the gut microbiome in MS patients. With the application of OMICS approaches, the researchers were able to successfully identify the pathophysiologic mechanisms of MS including the association of gut microbiome with meat consumption, activity and abundance of Th17 cells, and the levels of S-adenosyl-L-methionine (SAM). This longitudinal study suggests that the integration of the OMICS approach in assessing the pathophysiology of MS provides opportunities for the development of precision medicine for MS and improves the understanding of the etiology of MS. [63]

Omics approaches enable personalized treatment strategies for MS by identifying biomarkers that predict individual responses to disease-modifying therapies (DMTs). By elucidating molecular pathways, omics research reveals disease

heterogeneity, with transcriptomic studies showing distinct gene expression patterns across MS stages, informing treatment decisions and disease progression understanding. [64] Furthermore, specific protein biomarkers in cerebrospinal fluid (CSF), such as neurofilament light chain (NFL) levels, correlate with disease activity and progression, providing a reliable metric for monitoring disease trajectory and potentially guiding treatment optimization. [65, 66]

4. CONCLUSION

OMICS approaches tend to be beneficial for the identification of biomarkers of MS. The approaches include genomics, miRNAomics, proteomics, transcriptomics, and metabolomics. Identifying protein biomarkers, disrupted miRNAs, gene loci, and transcriptomes lay the foundation for understanding the etiology and pathophysiology of MS, a thorough understanding of which will allow healthcare professionals, researchers, and biotechnologists to formulate therapeutic interventions for MS.

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