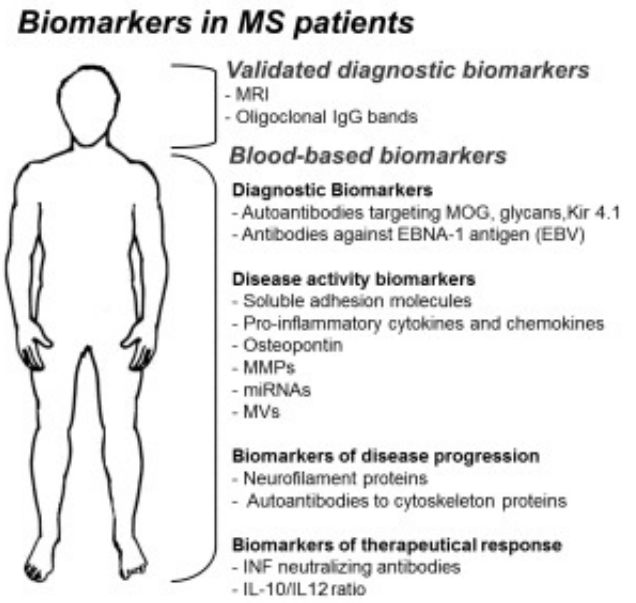
Blood-based biomarkers for multiple sclerosis

Multiple sclerosis (MS) is an immune-mediated, inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). MS is classified in: relapsing–remitting (RRMS), characterized by acute attacks followed by partial or complete recovery periods; primary progressive (PPMS), and secondary progressive (SPMS). Most RRMS at one point turns into a SPMS form, characterized by the irreversibility of the deficits due to progressive neurodegeneration; meanwhile, PPMS is characterized by a gradual progression of disability from the onset of the disease. Evidence suggests that MS is a multifactorial disease, resulting from a complex interaction between the environmental factors, the genetic background and the immune system. The complexity of its pathophysiological processes contributes to the highly variable course of the disease and unpredictable response to therapies.



The major focus of the research on MS is the identification of biomarkers in biological fluids, such as cerebrospinal fluid (CSF) or blood, to guide patient management reliably. Biomarkers are measurable indicators of pathogenic processes, or pharmacological responses to a therapeutic intervention. Because of the difficulties in obtaining spinal fluid samples, the research of blood-based biomarkers may provide increasingly important tools for clinical practice. Besides the only validated biomarkers for MS diagnosis (MRI of the brain and spine and oligoclonal IgG bands in CSF), serum autoantibodies could be potential diagnostic biomarkers. Antibodies against myelin oligodendrocyte glycoprotein (MOG) has emerged as a promising biomarker , especially in autoimmune pediatric demyelination and MS; meanwhile antibodies specific to glycans and a potassium channel (KIR4.1) expressed by astrocytes and oligodendrocyte, would be considered as a blood-derived diagnostic biomarkers in MS. There is considerable evidence that Epstein–Barr virus (EBV) infection could be an important causative factor in MS. Antibodies to EBV nuclear antigen (EBNA-1) seems to be associated with the highest MS risk. The activity of the disease is

associated with blood-brain barrier (BBB) damage and inflammation in RRMS. Among potential biomarkers associated with BBB damage there are: soluble adhesion molecules released from endothelial cells of BBB; meanwhile, among potential biomarkers associated with inflammation, there are: pro-inflammatory cytokines and chemokines, osteopontin involved in immune responses, matrix metalloproteases (MMPs) involved in migration of white blood cells to the CNS and other organs. The application of more advanced screening technologies has opened up new categories of biomarkers associated with MS activity, including microRNAs (miRNAs), non-coding single-stranded RNAs with function to modulate gene expression, and circulating microvesicles (MVs), shedding from BBB endothelial cells during inflammation. Neurodegeneration in PPMS or SPMS develops through multiple mechanisms, including exhaustion of functional compensation, mitochondrial injury, oxidative stress and altered expression of ion channels in demyelinated axons. Promising biomarkers for monitoring MS progression are serum neurofilament proteins and antibodies directed against the cytoskeleton. Recently, antigen microarray analysis, used to simultaneously characterize patterns of serum antibody reactivity in MS against a panel of CNS antigens, revealed unique autoantibody signatures, distinguishing RRMS, SPMS and PPMS from healthy controls and other neurologic diseases. Because of the wide availability of several therapeutic agents, the discovery of biomarkers to identify non-responder patients to drug therapy is essential in tailoring the best treatment. IFN-? (IFN) is one of the most widely used in MS treatment. Several serum molecules have been proposed as biomarkers for IFN therapy: IFN neutralizing antibodies, that have been found in 2%-45% of MS patients after IFN treatment; the IL-10/IL-12 ratio, that increases with IFN treatment in patients who respond to therapy. Even if several candidate biomarkers show promising potential both in reflecting clinical disease status and in monitoring treatment response, large and collaborative efforts will be needed to validate them for clinical application in MS.

Publication

Peripheral blood biomarkers in multiple sclerosis.
D'Ambrosio A, Pontecorvo S, Colasanti T, Zamboni S, Francia A, Margutti P
Autoimmun Rev. 2015 Dec