Newer Potential Pharmacological Targets for Multiple Sclerosis

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Abstract:
Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, and the most common cause is disability in young adults. Most patients have a relapsing–remitting course, and roughly half of them will eventually enter a degenerative progressive phase, marked by gradual actual of disability over time in the absence of relapses. Early initiation of treatment has delayed the onset of disability progression. Thus, there is increased interest in treating to target in MS, particularly targeting no evidence of disease activity. This review will describe the most common treatment goals in MS: potential pharmacological targets.. We will also cover how well current disease-modifying therapies achieve no evidence of disease activity, and discuss future options for improving MS treatment targets.

Key Words: Pharmacological targets, Multiple sclerosis, Relapsing remitting multiple sclerosis, Treatment goal, Disease activity, Disease modifying therapies.

INTRODUCTION:

Multiple sclerosis (MS) is a chronic illness involving your central nervous system (CNS). The immune system attacks myelin, which is the protective layer around nerve fibers.This causes inflammation and scar tissue, or lesions. (1)This can make it hard for your brain to send signals to the rest of your body.Multiple sclerosis (MS), the most prevalent neurological disability, is an autoimmune-mediated disorder that affects the central nervous system (CNS) and often leads to severe physical or cognitive incapacitation as well as neurological problems in young adult Multifocal zones of inflammation due to focal T-lymphocytic and macrophage infiltrations, and oligodendrocyte death are the primary causes of myelin sheath de- struction that result in the formation of CNS plaques composed of inflammatory cells and their products, demyelinated and transected axons, and astrogliosis in both white and gray matter. These lesions can cross-talk with the correct transmission of nerve impulses and lead to neuronal dysfunction such as autonomic and sensorimotor defects, visual disturbances, ataxia, fatigue, difficulties in thinking, and emotional problems Patients can manifest with a heterogeneous group of symptoms including changes in vision (unilateral visual loss, diplopia), weakness, dyscoordination, sensory loss or distortions, or changes in bowel and bladder function.(2) Less diagnostic but also disabling symptoms include cognitive change, fatigue, and mood disturbance. Progression of disease may eventually lead to severe disability. Many medications and other measures may be used to ameliorate MS symptoms. The availability of disease modifying therapies has revolutionized the care of patients with the inflammation of central nervous system is the primary cause of damage in MS. The specific elements that start this inflammation are still unknown(3).Studies have suggested that genetic, environmental and infectious agents may be among the factors influencing the development of MS. Many immunological studies have been done on the animal model for human MS known as the experimental autoimmune encephalomyelitis (EAE). Based on this model and observations of MS in humans, roles of several

immunological pathways involved in MS are being explored. (4)To understand these pathways it is important to first understand some basic points of the immune system in MS. While we have learned much about the immune system by the study of EAE, our lack of understanding of the differences between EAE and MS as well as the complexity of MS (and likely different immunologic subtypes of MS) must be kept in mind when reviewing experimental and immunologic data MS pathogenesis is considered to comprise 2 components: focal inflammatory demyelination and degeneration .(5)Available DMTs primarily are of benefit in controlling the inflammatory aspect of the disease; however, once the degenerative component starts, those therapies are less efficacious. In the pre-DMT era, natural history studies showed that patients with relapsing MS generally would require a cane to walk 150 m within 20 years of diagnosis.(6)

Newer Targets:Recent studies are now also focusing on memory B-cells (CD19+ and CD27+) which could have a role in modulating disease activity . Interestingly, DMTs classically considered acting via T cells (e.g. beta-interferons, glatiramer acetate, dimethyl fumarate, fingolimod, cladribine) were revealed to decrease the availability of B-cells to enter the CNS Furthermore, most B cells in MS lesions, meninges and ectopic B cell aggregates are CD27 antigen positive.(7) These are cell populations that have been shown to co-express latent EBV proteins and support a role for EBV infection in B-cell activation in MS brain . (8)This will need to be elucidated further .MTs' choice process; MS requires life-long management and DMTs have to fit with the personal history of each patient. For example, natalizumab (NTZ), an anti-α-4 integrin antibody induces peripheral memory B cell elevation but it is not associated with worsening of MS, and that could be due to the prevention of memory B cells entering the CNS . Likewise, the enhanced levels of peripheral memory B cells may contribute to rapid disease rebound after NTZ is withdrawn. Discontinuation of NTZ (usually for safety concerns, due to a high risk of progressive multifocal

leukoencephalopathy) is still a dramatic moment in MS therapeutic management and no guidelines exist about the ideal exit strategy. Therefore, the choice of CD20-depleting agents which reduce the high number of circulating B-cells could be useful. Data about treatment with rituximab post-NTZ revealed a lower relapse rates and also a reduced PML risk .(9)

Receptors Targets:The integrity of the blood-brain barrier is compromised during initial CNS inflammation, other mononuclear cells, including B cells and macrophages, penetrate into the CNS. B cells may have a dual role. B cells serve as APC and may expose additional myelin autoantigens, permitting the immune response to diversify.(10)Histamine receptors 1 and 2 (H2R) are present on inflammatory cells in EAE brain lesions, and histamine receptor genes confer susceptibility to EAE Encephalitogenic Th1 cells express more H1R and less H2R than Th2 cells. An H1R antagonist blocked EAE, and a PAFR antagonist reduced the severity of EAE. EAE was attenuated in mast cell-deficient mice.(11) Taken together, these data reveal involvement of elements associated with allergy in autoimmune demyelination. The role of mast cells presents a challenge to our understanding of the pathophysiology of these autoimmune disorders, previously thought to be diametrically opposite to allergy. Pathogenesis of demyelination must now be viewed as encompassing elements of both Th1 and "allergic" responses: allergy and autoimmunity are not antipodal.During CNS inflammation, glutamate is released by activated leukocytes and microglia. Glutamate excitotoxicity mediated by AMPA/kinate receptors causes damage to neurons and oligodendrocytes.One AMPA/kinate antagonist suppressed clinical EAE While treatment with this AMPA/kinate receptor antagonist did not alter CNS inflammation or proliferation by encephalitogenic T cells, treatment was associated with increased oligodendrocyte survival and reduced axonal loss.(12) These observations underscore the importance of identifying neuroprotective agents and developing strategies to promote oligodendrocyte differentiation.(13)

The potential candidate drugs (dorzolamide, iohexol, naringin,benzylpenicillin, cicloheximide, mycophenolic acid, GSK461364, dis-opyramide, H-89, 0175029–0000) enriched by the DEGs were identi-fied from the DSigDB database.Thus, a systems biology analytical pipeline was applied to identifybiomarkers signatures at protein levels (hub proteins, TFs) and RNAlevels (mRNAs, miRNAs) for MS from transcriptomics, expressedquantitative loci (cis-eQTL), protein-protein interaction (PPI), DEGs-TFs, and DEGs-miRNAs interactions data. Geneset enrichment analyseswere used for gene ontology (GO) and pathways enriched by the DEGs.Candidate drugs targeting identified biomarkers were also identifiedbased on the gene signatures. In sum, the present study employed asystems biology approach to reveal molecular signatures comprisingbiomolecules at the protein level (hub protein, TFs), RNA levels(mRNAs, miRNAs), with pathways to

provide an in-depth under-standing of the mechanisms of pathogenesis in MS.

Targeting Central Nervous System:
The blood-CNS barrier (BCNSB) is a dynamic and complex cellular system that separates the CNS from the bloodstream. It does this by strictly controlling the exchange of both cells and molecules between the two compartments . The largest surface area for exchange is the blood-brain barrier (BBB), which separates the bloodstream and the brain.(14) Its sister barrier, the blood-spinal cord barrier (BSCB), separates the bloodstream and the spinal cord. There is also an epithelial cell barrier separating the bloodstream and the cerebrospinal fluid (CSF) at the choroid plexus and the arachnoid villi. Both the BBB and the BSCB comprise the endothelial cells of CNS blood vessels, along with a thick basement membrane and astrocytes. They display a unique phenotype characterized by the presence of endothelial cells that are connected by an intercellular adhesion complex. This forms the close contact between the adjacent cells known as tight junctions.This barrier function of the BCNSB is further enhanced by the relative paucity of fenestrae and pinocytotic vesicles. The BCNSB has two further barrier elements: (i) a metabolic barrier that contains a complex array of enzymes (including acetylcholinesterase, alkaline phosphatase, γ-glutamyl transpeptidase, and monoamine oxidases) that degrade different chemical compounds thus altering their pharmacological activity and (ii) a transport barrier that contains a variety of efflux transporters, including P-glycoprotein and breast cancer resistance protein .

Tight junctions are the critical component of the BCNSB as they control paracellular diffusion and maintain the structural and functional polarity of the specialized endothelial cells of the BBB and BSCB. Thus, the BCNSB contributes to the homeostasis of the parenchyma of the brain and spinal cord and provides protection against many toxic compounds and pathogens Indeed, the BCNSB is largely impermeable to compounds that are not lipophilic and have a molecular weight greater than 450 Da This presents a major challenge for CNS drug discovery .

The Role of the Immune System in MS
There are two general types of immune response: innate and adaptive. The innate system plays a role in both the initiation and the progression of MS by influencing the effector function of T and B cells .Thus, for example, through the activation of specific (mainly toll-like) receptors in an antigen nonspecific manner, dendritic cells become semi mature and induce regulatory T cells to produce inhibitory cytokines such as IL-10 or tumour necrosis factor-γ. As the dendritic cells mature, they polarize CD4+ T cells to differentiate into Th1, Th2, or Th17 phenotypes; it is the Th1 phenotype that promotes inflammation.

CONCLUSION:

Unlike nearly all other blood vessels in the body, the endothelial cells of the BCNSB are bound together by tight junctions. This means that a neuroactive compound needs to take a transcellular route across the BCNSB in order to enter the CNS. These tight junctions, coupled with numerous efflux transporters and metabolizing enzymes, constitute a formidable barrier to the movement of both molecules and cells from the bloodstream into the CNS. The BCNSB plays a role in MS and its treatment at three levels.Pathophysiology. The movement of activated leukocytes across the BBB is a key event in the pathophysiology of MS.

Drug-induced pathophysiology. Natalizumab blocks immunological surveillance of the CNS, leaving the CNS immunocompromised. A detrimental consequence of this is the reactivation of the JC virus in the brain which can then lead to progressive multifocal leukoencephalopathy (PML).

MS pharmacotherapy. Most MS medicines are biological drugs and so their large size prevents their movement across the Blood central nervous system barrier

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