Demyelination and remyelination signalling in multiple sclerosis as an aid to targeted therapy

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) characterised by demyelination. Demyelination, i.e. damage and erosion of the myelin sheath which protects the nerve fibres, occurs in the white matter of the brain leading to the formation of plaques or scleroses. Demyelination is thought to be caused by antibodies generated against myelin components and T- cell mediated autoimmune responses. The immunoglobulins or autoantibodies in the cerebrospinal fluid display a unique isoelectric banding pattern known as oligoclonal bands (OCBs).

MS is generally regarded as an autoimmune condition, but not infrequently the concept has been debated. There is overwhelming evidence that humoral factors contribute to the process of demyelination in both the peripheral and the central nervous system. Therapeutic modulation of immune responses has been a valuable approach in combating bacterial infections and the response to autoantigens. Immunomodulation can be achieved by a dual strategy of antibody mediation and of employing immunomodulatory drugs. Antibodies targeting T cell epitopes or aimed at B-cell signalling involved the regulation of their proliferation and differentiation have been in vogue. The deployment of immunomodulatory drugs forms another arm of treatment strategy. Currently both approaches have been adopted in the management of MS patients.

Many demyelinating diseases of the CNS have been studied from the point of view of identifying and defining the clinical and subsidiary and sub-clinical parameters including genetic markers and their downstream effector products with reference to demyelination and disease progression. The development and evolution of targeted therapy to any disease requires the identification of targets amenable to treatment of patients, location of nodes of deregulation and dysfunction of the signalling pathways in order to devise strategies of drug development for targeted intervention. Hence the focus here is mainly on ways and means to prevent demyelination and promote the process of remyelination.

The OCBs relate to the disease course and progression and the OCB patterns can be linked with the expression of angiogenic molecular species. Molecular approaches to define the genesis and significance of OCBs, elucidation of their perceived link with angiogenic signalling and to the severity of the disease suggest that tangible outcome can be expected since angiogenic agents can determine the disease course, progression and severity. Angiogenic signalling which has also been implicated in demyelination could provide the valuable option of using angiogenesis inhibitors in disease control.

Prominently, the constituents of the PI3K (phosphoinositide 3-kinase)/Akt axis might be key elements in myelination with its demonstrable links with mTOR (mammalian target of rapamycin) mediated transcription of downstream target genes. Inflammatory signals and innate and acquired

immunity possibly devolving from the activation of NF-?B (nuclear factor ?B) responsive genes might be highly relevant in the context of MS. NF-?B signalling has been implicated in myelination. The transcription factor STAT (signal transducers and activators of transcription) and the EBV (Epstein-Barr virus) transcription factor BZLF1, which contribute significantly to the disease process, are a major environmental factor linked to MS. EBV can activate TGF (transforming growth factor) and VEGF (vascular endothelial growth factor) signalling. Furthermore, EBV microRNAs could be putative signalling mediators of pathogenesis.

Stem cell transplantation therapy has lately gained much credence, so the current status of mesenchymal and hematopoietic stem cell therapy is reviewed with emphasis on the differential expression immune-related genes and operation of relevant signalling systems. Stem cell therapy has been often advocated for neuro-regeneration and remyelination for they modulate the immune system using NF-?B and STAT transcription factors. The accent placed in this article on remyelination is motivated by the contingency that the current treatment modalities are mainly directed towards the control of demyelination.

Gajanan V Sherbet

Publication

Molecular approach to targeted therapy for multiple sclerosis.
Sherbet GV.
CNS Neurol Disord Drug Targets. 2015 Nov 10