Molecular insights into the immunopathology of multiple sclerosis: From myelin destruction to repair.

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Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neurodegeneration. It primarily affects young adults and is a leading cause of non-traumatic neurological disability. The immunopathology of MS reflects a complex interplay between the immune system and the CNS, resulting in damage to myelin—the protective sheath surrounding nerve fibers—and, ultimately, axonal injury. Recent molecular insights have significantly enhanced our understanding of MS pathogenesis and the mechanisms underlying both myelin destruction and repair.

At the core of MS immunopathology is an autoimmune response against CNS myelin components, most notably myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). In genetically susceptible individuals, environmental triggers such as viral infections (e.g., Epstein-Barr virus) or vitamin D deficiency may initiate an aberrant immune response. Autoreactive CD4+ T helper cells, particularly Th1 and Th17 subsets, cross the blood-brain barrier (BBB) and infiltrate the CNS. Th1 cells release interferon-gamma (IFN-γ), while Th17 cells produce interleukin-17 (IL-17), both of which activate microglia and attract other inflammatory cells [1-5].

The infiltration of CD8+ cytotoxic T cells, B cells, macrophages, and dendritic cells amplifies the immune response. CD8+ T cells directly target oligodendrocytes and neurons, while B cells produce autoantibodies that contribute to myelin damage through antibody-dependent cytotoxicity and complement activation. The presence of oligoclonal bands in the cerebrospinal fluid (CSF) of MS patients is a hallmark of this ongoing B-cell activity.

Microglia and infiltrating macrophages release reactive oxygen species (ROS), nitric oxide, and pro-inflammatory cytokines such as TNF-α and IL-1β, which exacerbate tissue damage. This inflammatory milieu leads to demyelination—stripping away of the myelin sheath—which impairs saltatory conduction along axons, resulting in the characteristic neurological deficits of MS. Axonal transection, seen in chronic lesions, contributes to irreversible neurodegeneration and disease progression[6-10].

However, the CNS also possesses mechanisms for myelin repair, a process known as remyelination. This is primarily mediated by oligodendrocyte precursor cells (OPCs), which proliferate, migrate to demyelinated areas, and differentiate into mature oligodendrocytes capable of synthesizing new myelin. Molecular regulators of remyelination include growth factors such as brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF), and insulin-like growth factor-1 (IGF-1). Unfortunately, in progressive MS, remyelination often fails due to chronic inflammation, oxidative stress, and the inhibitory environment within MS plaques.

Recent advances in molecular biology, including single-cell RNA sequencing and proteomics, have uncovered specific gene expression patterns associated with both damage and repair processes in MS. For example, molecules like LINGO-1, which inhibit OPC differentiation, have become targets for therapeutic intervention. Monoclonal antibodies targeting B cells (e.g., ocrelizumab) and sphingosine-1-phosphate receptor modulators (e.g., fingolimod) modulate immune activity and help preserve myelin integrity.

Conclusion

In conclusion, the immunopathology of MS is driven by a multifaceted immune attack on CNS myelin, mediated by both cellular and humoral mechanisms. Understanding the molecular basis of myelin destruction and the barriers to repair has opened new avenues for disease-modifying therapies, offering hope for improved outcomes and potential reversal of neurological damage in MS patients.

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