Multiple sclerosis (MS), as one of the most important diseases of the central nervous system (CNS), is characterized by multiple areas of inflammation and demyelination in the white matter of the brain and spinal cord. The clinician manifestations are protean, determined by the various locations and extent of the CNS demyelinating lesions, characterized by infiltration of mononuclear cells, the proliferation of macrophages, and loss of oligodendrocytes, myelin-producing cells. In this article, Chinese authors investigated the unrecognized role of autoreactive T-cells in the bone marrow of patients with multiple sclerosis, as the primary site of hematopoiesis.

In relapsing-remitting MS, immune cells that infiltrate the CNS are primed in the periphery and reactivated in the CNS by local antigen-presenting cells. Macrophage-type cells are considered the most important antigen-presenting cells in the inflammatory lesions of MS, MS plaques, and true effectors of the clinical and pathological expression of the disease. Upon entry into the CNS, autoreactive T-cells induce a cascade of cytokines and chemokines, which recruit hematogenic myeloid cells, neutrophils, and monocytes. The massive CNS infiltration with leukocytes suggests their rapid consumption from peripheral reserves, which are limited and dynamic production and supply from the bone marrow.

Chemokines are small proteins that attract different cytokines, cells, and substances to specific sites. Depending on the number of amino acids between the first two cysteine residues, the chemokines are classified into four subfamilies, CXC, CC, CX3C, and XC. Although most inflammatory cells express the CCL5 chemokine with the highest affinity for the receptor CCR5, T-cells and monocytes are the most common cell types that express CCL5. Chemokine CXCL12, i.e. stromal cells- derived factor-1, is a key factor derived from bone marrow stromal cells. This chemokine binds to its cognate receptor CXCR4 and attracts the target cells to bone marrow.

About the study

The research team performed a single-cell analysis of bone marrow biopsy samples obtained from treatment-naive MS patients. The analysis demonstrated that autoreactive T-cells migrate into the bone marrow *via* the CXCL12- CXCR4 axis. Researchers then used a mouse model of MS, experimental autoimmune encephalomyelitis, and confirmed *in vivo* that the CXCL12-CXCR4 axis is necessary for autoreactive T-cells to migrate into the bone marrow.

To understand how autoreactive T-cells induce myelopoiesis in the bone marrow of MS patients, scientists quantified the factors derived from T-cells residing in the bone marrow. They found that CD4+ T-cells among 113 cytokines measured, highly expressed the cytokine CCL5, called RANTES. This confirmed that T lymphocytes residing in the bone marrow are a major source of CCL5.

The authors believe that autoreactive T-cells augment myelopoiesis (but not lymphopoiesis) of hematopoietic stem and progenitor cells involving the CCL5-CCR5 axis. Consequently, myelopoiesis increases the number of bone marrow myeloid cells which can invade the CNS and accelerate inflammation and demyelination.

Conclusion

Although the current understanding of the role of autoreactive T lymphocytes in MS pathogenesis is focused on their expansion into lymphoid organs and penetration into the CNS, this study revealed that the bone marrow, as the primary site of hematopoiesis, has an

unrecognized role in MS, promoting intimate interactions between autoreactive T-cells and hematopoietic cells.

The authors concluded that these findings highlight the role of myelopoiesis in the development of autoimmune encephalomyelitis. Additionally, these results could provide a therapeutic opportunity for MS by restricting the migration of autoreactive T lymphocytes into bone marrow and suppressing harmful myelopoiesis in MS.

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