ROLE OF CHEMOKINES AND PI3KGAMMA IN MEDIATING LEUKOCYTE MIGRATION INTO THE CENTRAL NERVOUS SYSTEM.

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The influx of leukocytes into the central nervous systems contributes to physiopathology of several chronic inflammatory diseases, including multiple sclerosis, and infectious diseases, such as cerebral malaria and herpesvirus infection. We have been interested in trying to dissect the mechanisms underlying leukocyte recruitment into the brain and in evaluating the relevance of leukocyte recruitment for brain damage and dysfunction. More specifically, we have focused on the role of chemokines in mediating leukocyte influx. Chemokines are a class of chemoattractant cytokines that activate seven-transmembrane receptors on the surface of leukocytes leading to their adhesion and subsequent migration into tissue. In the context of multiple sclerosis, we have found that levels of the chemokine CCCL2 are diminished in cerebrospinal fluid (CSF) and increase with treatment with high dose steroids. In an experimental model of experimental autoimmune encephalomyelitis (EAE) in mice, there is brain inflammation that correlated with enhanced interaction of leukocytes with endothelial cells, as assessed by intravital microscopy. Levels of CCL2 were elevated in brain tissue and blockade of CCL2 with an anti-CCL2 antibody or a chemokine antagonist prevented leukocyte/endothelial cell interactions and overall brain pathology. Bradykinin B2 receptors were important for the production of CCL2, leukocyte adhesion and disease progression, as assessed by experiments in B2-deficient mice. Experiments in PI3Kgamma-deficient mice suggest that this enzyme appears to mediate leukocyte recruitment into tissue and activation, but does not participate in leukocyte rolling or adhesion. In a model of cerebral malaria caused by infection with *Plasmodium berghei* ANKA, we could also observe significant leukocyte-endothelial cell interactions, as assessed by intravital microscopy, which correlated with disease activity and lethality. Levels of CXCL9, CCL2 and CCL5 were elevated in brain and correlate with peak leukocyte adhesion. The role of these chemokines is currently under evaluation. Overall, these studies highlight the important role of chemokines in mediating inflammation in the CNS and suggest that induction of leukocyte adhesion appears to be a major mechanism by which these mediators participate in the physiopathology of various brain disorders.

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