

LCMV infection of perforin-deficient mice. In this model, IFN γ production is required, presumably causing macrophage activation, and the presence of CD8 cells is essential. Alternative macrophage activation, as induced by IL-4 or IL-13, can lead to significant tissue inflammation. We investigated the possible roles of IL-4 and IL-13 in the induction of histiocytosis and/or hemophagocytosis. We found that exposure to high levels of IL-4, through an implanted minipump or administration of IL-4/anti-IL-4 immune complexes, leads to substantial histiocytosis and erythrophagocytosis within the liver and spleen, to bone marrow erythrophagocytosis, and to acute weight loss. The accumulated macrophages are YM1 positive, indicating alternative activation. This effect is not dependent on the presence of antibody or T-cells, as treatment of Rag 2 $^{-/-}$ mice leads to similar disease. IL-4 treatment results in suppression of serum IL-12, elevation of IFN γ , IL-10 and KC (the mouse IL-8 analogue), with no change in the proinflammatory cytokines IL-6, IL-1 β or TNF α . IFN γ neutralization during IL-4 treatment exacerbates histopathology. Interestingly, IL-13 treatment, while leading to bile duct YM1 upregulation, serum KC elevation, and serum IL-12 suppression, causes no hemophagocytosis or histiocytosis. Taken together, these data describe a novel pathophysiologic pathway for histiocytic/erythrophagocytic disorders involving acute specific elevation in IL-4 and alternative macrophage activation.

doi:10.1016/j.clim.2009.03.094

OR.80. Oncostatin M is a Potent Inducer of CNS Inflammation

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The neuropoietic cytokine oncostatin M (OSM) is expressed in MS lesions, but its function during CNS lesion development is unknown. In order to elucidate the effects of OSM in the CNS, we have induced local expression of mouse OSM in the CNS of C57/BL6 mice by means of lentiviral vectors and compared the effects of OSM to those of local expression of another neurokinin family member leukemia inhibitory factor (LIF). We found that at sites of OSM expression, substantial tissue remodelling occurs, the blood-brain barrier (BBB) is disrupted and serum leaks into the CNS parenchyma. Endothelial cells of the BBB showed a dramatic upregulation of adhesion molecules. None of these effects were detected after CNS-directed expression of LIF. Moreover, local expression of OSM in the healthy CNS induced a strong expression of MHCII and attracted large amounts of T-cells and macrophages/microglia to the CNS. Our study identified OSM as a pathological neurokinin with the potential to induce neuroinflammation in the healthy CNS.

doi:10.1016/j.clim.2009.03.095

OR.81. Astrocyte-secreted Sonic Hedgehog Supports CNS Anti-inflammatory Activity and Promotes Optimal Human Blood Brain Barrier Functioning

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The blood-brain barrier (BBB) is composed of tightly bound endothelial cells (ECs) that control the entry of blood-borne molecules and immune cells into the CNS. BBB-ECs are surrounded by astrocyte endfeet known to regulate BBB permeability. Recent studies indicate that components of the Hedgehog (Hh) pathway play an important role in vascular proliferation, differentiation and tissue repair in adult tissues. As BBB disruption is early observed in neuroinflammatory conditions such as Multiple Sclerosis (MS), this study aims to demonstrate that astrocyte-secreted Sonic Hh (Shh) contributes to the maintenance and repair of BBB functions. Our experiments show that human astrocytes express and secrete Shh and conversely, that human BBB-ECs bear the Hh receptor Patched-1, the signal transducer Smoothened (smo), as well as transcription factors of the Gli family. Furthermore, we show that activation of the Hh pathway in BBB-ECs restricts the passage of soluble tracers, decreases the surface expression of ICAM-1, and the secretion of the pro-inflammatory chemokines IL-8/CXCL8 and MCP-1/CCL2. The migration of CD4 $^{+}$ lymphocytes is also reduced after BBB-EC treatment with Shh and Hh pathway agonists. In vitro stimulation of BBB-ECs with TNF- α and IFN- γ decreases the mRNA expression of Patched-1, Smo and Gli-1, thus deregulating the Hh signaling pathway and preventing the barrier stabilizing properties of Hh. Our data provide strong evidence for an anti-inflammatory and BBB-promoting effect of astrocyte-secreted Shh and suggest that a pro-inflammatory environment disrupts the BBB by impacting, at least in part, on Hh signaling in CNS ECs.

doi:10.1016/j.clim.2009.03.096

OR.82. Pro-inflammatory Cytokines Mediate Regression of Autoimmune Arthritis Induced by Th1/Th17 Cells

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Autoimmune arthritis is considered to be a T helper 1 (Th1)-mediated inflammatory disease. The precise target antigen in rheumatoid arthritis is not yet defined, but studies in the adjuvant-induced arthritis (AA) model have implicated heat-shock protein 65 (Hsp65) as one of the targets of autoimmune response. Over the past two decades, the Th1-Th2 paradigm of immune regulation has been the cornerstone of understanding the interplay among various effector