TGF-beta receptor II gene deletion in leucocytes prevents cerebral vasculitis in bacterial meningitis

Summary / Zusammenfassung
In bacterial meningitis, the chemokines macrophage inflammatory protein-2 (MIP-2 / CXCL2) and Groalpha / CXCL1 lead to recruitment of leukocytes into the central nervous system (CNS). At the site of infection in the meninges and cerebrospinal fluid, leukocytes release reactive oxygen intermediates (ROI), tumor necrosis factor alpha (TNFalpha) and interleukin-1beta (IL-1beta). Although these cytokines assist in clearance of bacteria, they also result in neuronal injury associated with meningitis. Transforming growth factor beta (TGFbeta) is a potent deactivator of polymorphonuclear leukocytes (PMN) and macrophages since TGFbeta suppresses the production of ROI, IL-1 and TNFalpha. Our recent data show that deletion of the TGFbeta receptor II gene in PMN enhances recruitment of PMN into the CNS of mice with S. pneumoniae meningitis. This was associated with more efficient clearance of bacteria, and almost complete prevention of intracerebral necrotizing vasculitis and stroke. Thus the endogenous production of TGFbeta in bacterial meningitis may result in an impairment of innate immunity. Lower PMN recruitment in control mice was not due to low concentrations of the chemokines MIP-2 / CXCL2 and Groalpha / CXCL1 in the CNS. Future research will focus (1) on the mechanisms leading to TGFbeta induced impairment of PMN recruitment into the CNS and (2) on the TGFbeta controlled pathways which provoke vasculitis and stroke in bacterial meningitis. Mice infected with S. pneumoniae will be treated with TGFbeta blocking agents such as anti-TGFbeta antibodies or small molecules which inhibit TGFbeta receptor II to phosphorylate and activate TGF receptor I. By this approach it should be possible to mimic the beneficial effect which we have observed in S. pneumoniae infected mice which have an inactivation of the TGFbeta receptor II gene.

Publications / Publikationen

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