Potential role of brain pericytes in the innate immune response to pneumococcal central nervous system infection

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Background: Pneumococcal meningitis is a serious infectious disease of the CNS. Pneumococcal infection generates a massive inflammatory reaction which is largely responsible for meningitis-associated brain damage. There is still great uncertainty about the cellular initiators of this inflammatory response. Experimental work provided evidence that postcapillary venules are the primary site of CNS entry for pneumococci and leukocytes. Postcapillary venules consist of specialized endothelial cells attached to a basement membrane. Embedded in the basement membrane are pericytes. The vessels are surrounded by a fluid-filled space populated by immunocompetent cells like macrophages and mast cells. Recent studies show no or only partial effects of mast cell deficiency or macrophage depletion in mouse models of PM, suggesting contribution of additional cells residing in the perivascular niche to immune activation upon pneumococcal CSF infection.

Materials/methods: Primary murine and human brain pericytes were exposed to different concentrations of pneumococci (D39 strain) and different serotypes in the absence or presence of selected Toll-like receptor (TLR) antagonists. Cytokine and chemokine release as well as cell viability were monitored by commercially available kits. To get a first hint whether pneumococcal meningitis is associated with changes in the brain pericyte population, we also conducted immunohistochemical analysis on brain sections obtained from healthy and infected mice. To label pericytes, we stained for the pericyte markers CD13 or PDGFRbeta.

Results: Both, murine and human pericytes responded to pneumococcal challenge by altered cytokine and chemokine release (e.g., an increased interleukin-6 liberation as compared to uninfected cells). This response varied substantially between different pneumococcal serotypes. By using an inhibition strategy, we found evidence that pericytes recognize the presence of pneumococci by means of TLR, namely TLR2 and endosomal TLR. In the mouse model, (vessel-associated) PDGFRbeta immunoreactivity appeared regionally disrupted, sometimes patchy and was missing at some vascular segments at 24 hours post infection. At 48 hours post infection, patchy and missing PDGFRbeta expression was still detectable. The staining pattern for CD13 largely resembled that for PDGFRbeta.

Conclusions: Based on these data, we hypothesize that pericytes could be both effector and target cells in the pathogenesis of pneumococcal meningitis.