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Role of mast cells in pneumococcal meningitis

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Background: Pneumococcal infection of the leptomeninges generates a powerful inflammatory reaction which contributes essentially to meningitis-associated brain damage. Although the major effector cells of tissue injury in meningitis and the mechanisms underlying their invasion into the leptomeninges have been largely characterized, there is still uncertainty about the cellular initiators of the massive leptomeningeal inflammatory reaction. The leptomeninges are densely populated with mast cells. *In vitro*, a human mast cell line has been shown to respond to pneumococcal challenge by degranulation. Thus, we hypothesized involvement of mast cells in pneumococcal meningitis.

Material/methods: Murine mast cells derived from bone marrow cells of wild type-, MyD88/TRIF-, and TLR2-/TLR13- knockout mice were exposed to *Streptococcus (S.) pneumoniae* (serotype 2, 3, 7F, 19A) and assessed for degranulation by measuring the release of beta-hexosaminidase and for cytokine production by ELISA. In supplemental experimental series, wild type mast cells were challenged with *S. pneumoniae* and concomitantly treated with diverse pattern recognition receptor antagonists (e.g., anti-Toll-like

receptor [TLR] 2 and TLR4 antibodies and chloroquine). Moreover, the phenotype (like cerebrospinal fluid (CSF) leukocyte counts and clinical score values) of two mast cell-deficient mouse strains (namely Kit(W/W-v) and Kit(W-sh/W-sh) mice) was evaluated in an established meningitis model.

Results: Murine bone marrow-derived mast cells degranulated upon stimulation with *S. pneumoniae* and showed increased CC-chemokine ligand 2 (CCL2) and interleukin (IL)-6 production. Pneumococci-induced mast cell activation was dependent on the presence of pneumolysin and varied substantially between different serotypes. Genetic deletion of Myd88/TRIF which causes a complete loss of Toll-like receptor (TLR) signaling leads to a significantly diminished release of both, hexosaminidase and cytokines/chemokines. Supplemental experiments using different TLR antagonists (e.g., anti-TLR2 antibodies and chloroquine) as well as TLR-deficient mast cells suggested a role of nucleic sensing TLRs in mast cell activation upon exposure to *S. pneumoniae*. In the meningitis model, both mast-cell deficient mouse strains had significantly increased CSF leukocyte counts, as compared to the respective infected wild type strains (e.g., in Kit(W-sh/W-sh) mice: 23,240 +/- 4,637 vs. 15072 +/- 4928 cells/microl). Mast cell reconstitution resulted in a partial reversal of this effect (e.g., in Kit(W-sh/W-sh) mice to 19,119 +/- 5335 cells/µl). However, there were no significant differences between infected wild type and mast-cell-deficient mouse strains with regard to loss of body weight and temperature, bacterial titres in blood and brain, CSF interleukin-1beta levels, and clinical score values.

Conclusions: Despite murine bone marrow-derived mast cells are activated by *S. pneumoniae in vitro*, we conclude that they do not or only to a minor extent influence the *in vivo* manifestations of intracisternal *S. pneumoniae* infection.