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Dissertations-Kurzfassung

Function of Tumor Necrosis Factor and Toll-Like Receptors 2and 4 in murine cerebral listeriosis

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Tumor necrosis factor (TNF) and Toll-like receptors (TLR) play an important role in infectious diseases, but the precise role in cerebral listeriosis is still unclear.
The aim of the present experimental study was to define the cellular sources and kinetics of TNF in cerebral listeriosis, to define the functional role played by brain- and hematogenously-derived TNF for pathology control and to clarify the impact of TNF on homing and frequency of CD4+ and CD8+ *Listeria*- specific T cells in cerebral listeriosis.
Non-immunized and immunized $TNF^{-/-}$and WT mice were i.c. infected with either *DactA L. monocytogenes* or OVA *DactA L. monocytogenes*. For both, non-immunized and immunized WT mice, microglia was identified as a major brain–resident cell population producing TNF early after infection (day 1 to day 3). In addition, macrophages and at later times, CD4+ and CD8+ T cells contributed to i.c. TNF production. Following i.c. infection with *DactA* or OVA *DactA L. monocytogenes* both non-immunized and immunized $TNF^{-/-}$ mice were more susceptible to cerebral listeriosis than WT animals and exhibited an increased mortality rate. The more severe course $TNF^{-/-}$ mice was explained by the important role of TNF for an efficient i.c. control of *Listeria*. Reciprocal bone marrow between $TNF^{-/-}$ and WT showed that hematogenously produced TNF is absolutely essential for survival of cerebral listeriosis, whereas brain–derived TNF plays a less important role. Furthermore, TNF is not required for the recruitment and the persistence of CD4+ and CD8+ T cells in the brain of mice with cerebral listeriosis. In contrast, TNF influences the kinetics and frequency of *Listeria*-specific CD4+ and CD8+ T cells and the surviving immunized $TNF^{-/-}$ had increased frequencies of i.c. *Listeria*-specific CD4+ and CD8+ T cells.
In addition, the impact of TLR2 and TLR4 on the pathogenesis of cerebral listeriosis was analysed. Following i.c. infection with OVA *L. monocytogenes* (a more virulent strain than *DactA* or OVA *DactA L. monocytogenes*) non-immunized $TLR2^{-/-}$, $TLR4^{-/-}$ and WT mice succumbed withouth differences regarding time of death. An active i.p. immunization with OVA *L. monocytogenes*, provided some protection against i.c. challenge in all experiemntal groups without any differences. Moreover, *Listeria* replicated equally strong in all experimental groups. In contrast to $TLR4^{-/-}$ and WT mice, $TLR2^{-/-}$ mice recruited a significantly reduced number of leucocytes to the brain. Histopathology revealed that TLR2 mice had no selective effect on the recruitment of leucocytes to certain regions of the brain. Collectively, these data suggest that TLR2 and TLR4 play no essential role for the control of i.c. *Listeria*, but that TLR2 is involved in the regulation of leucocyte recruitment to the brain.