IJAE
Vol. 116, n. 1 (Supplement): 81, 2011
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Microglia polarization and inflammatory challenges

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A wealth of recent evidence indicates that microglia activation is a polarized process, leading to a potentially neurotoxic M1 "classical activation" or potentially neuroprotective M2 "alternative activation". The regulation of this process is, however, still largely unknown. We here investigated the induction of molecules which characterize M1 and M2 microglia responses after systemic (ip) and central (intracerebroventricular, icv) exposure to lipopolysaccharide (LPS). These challenges elicit different inflammatory responses of the brain parenchyma; in particular, leukocyte infiltration in the brain occurs after icv but not after ip LPS exposure. Young adult mice were subjected to ip or icv LPS injection, sacrificed at different time points from 2h up to 10 days, and compared with matched saline-treated control mice. Analyses with the pan-T cell marker CD3 confirmed the occurrence of T cells in the brain parenchyma after icv but not after ip LPS injections. Immunohistochemical phenotyping of microglia was pursued to reveal major histocompatibility complex class II (MHCII) antigen, a key molecule in M1 activation, and chitinase 3-like 3 (YM1), part of the M2 molecular repertoire. The M1 type of microglial response, revealed by upregulation of MHCII immunosignal, was very intense and occurred during the first 24h, with a peak at 2h after icv LPS, and at 6h after ip LPS. The M2 type of response, revealed by YM1 immunoreactivity in some microglial cells, followed the M1 type response evolving in the days which followed the first 24h, with an earlier peak (at 5 days) and more marked persistence (up to 10 days) after icv LPS, i.e., in the presence of T cell infiltration. Altogether the findings point out dynamic processes of microglia activation and its polarization over time, and a microglia – T cell dialogue with potential neuroprotective effects of T cell recruitment. Further investigation on the profiling of the M1 and M2 types of microglia activation, and of the possible molecules implicated in the microglia – T cell dialogue will further enlighten these crucial polarization mechanisms.

Keywords: microglia, neuroinflammation, M1, M2