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Primed monocytes in gamma-herpesvirus-induced EAE exacerbation

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Purpose: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). MS is a multifactorial disease caused by genetic, immunological and environmental factors. The most strongly associated environmental risk factor for MS is Epstein-Barr virus (EBV), for which it is still unclear how it contributes to disease development. While most studies on EBV and MS focus on lymphocytes, here the contribution of EBV-imprinted myeloid cells to MS development is investigated.
Methods: Experimental autoimmune encephalomyelitis (EAE) is induced in mice pre-infected with Murid Herpesvirus 4 (MuHV-4). Phenotypic changes of CNS infiltrating immune cells are determined by flow cytometry. To find human translation, the phenotype of monocytes of EBV seropositive and negative donors are compared.
Results: A significantly worse EAE outcome and an increase in CNS infiltrating immune cells were found in pre-infected mice. MuHV-4 infection led to a high activation status of monocytes in blood, shown by an upregulation of MHC-II, Sca-1, CD86, Saa3 and CXCL9 and this phenotype remained present after the lytic infection phase. After EAE induction, an increased infiltration of these monocytes is found in the CNS of MuHV-4 infected mice. Also, highly activated microglia are seen after MuHV-4 infection. EBV seropositivity in humans altered the phenotype of monocytes resulting in more CXCL9 and CCR2, while reducing the anti-inflammatory phagocytosis receptor CD93 and the myelin scavenger receptor CD36. MuHV-4 infected mice show a similar disease aggravation after adoptive transfer of MOG35-55 T cells, further indicating that the observed MuHV-4-mediated EAE aggravation is not directly mediated by T cells. Finally, monocyte depletion during EAE diminished clinical symptoms to the level observed in non-infected mice without affecting T cell phenotype, indicating a causative role of monocytes in MuHV-4-mediated EAE exacerbation.
Conclusion: EBV mediated priming of the myeloid cell compartment is seen in both humans and mice and leads to worse disease. Future research in this understudied field focuses on what myeloid changes worsen disease symptoms and thus provide support for EBV targeted interventions.

