**CpG type-A induction of an early protective environment in experimental multiple sclerosis**

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Experimental autoimmune encephalomyelitis (EAE) is an inflammatory, demyelinating disease of the CNS that mimics human multiple sclerosis (MS), and it is thought to be driven by Th1 and Th17 myelin-reactive cells. Although adaptive immununity is clearly pivotal in the pathogenesis of EAE – with an essential role of CD4+ T cells – little is known of early, innate responses in this experimental setting. CpG-rich oligodeoxynucleotides (ODNs), typically found in microbial genomes, are potent activators of TLR9 in plasmacytoid dendritic cells (pDCs). In this study, we compared the effects of two types of CpG, namely, type A and type B, on EAE. We found that treatment with CpG type-A ODN (CpG-A) – known to induce high amounts of IFN-α in pDCs – significantly reduced disease severity in EAE, relative to controls (12.63 ± 1.86 vs. 23.49 ± 1.46, respectively; p = 0.001). Treatment also delayed onset of neurological deficits and reduced spinal cord demyelination, while increasing the percentage of splenic regulatory (Foxp3+ CD4+) T cells. CpG-A likewise reduced the levels of IL-17 and IFN-γ in the CNS. Mechanistic insight into those events showed that CpG-A promoted a regulatory phenotype in pDCs. Moreover, adoptive transfer of pDCs isolated from CpG-A–treated mice inhibited CNS inflammation and induced disease remission in acute-phase EAE. Our data thus identify a link between TLR9 activation by specific ligands and the induction of tolerance via innate immunity mechanisms.