The role of B cell-derived IL-10 in regulation of chronic CNS inflammation

Short title: B cell-derived IL-10 in chronic CNS disease

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Background
Several lines of evidence indicate essential roles for B cells in the pathogenesis of multiple sclerosis (MS). B cells act as potent antigen-presenting cells (APCs) and throughout the chronic course of MS, B cell-follicle like structures can be found in the meninges of MS patients. However, whether and how B cells interact with microglia to possibly modulate chronic progression of MS remains unclear.

Aims
We aimed at analyzing the interaction of B cells with microglia in modulation of chronic CNS inflammation.

Methods
Primary microglia were generated from newborn mice and were cultured with activated B cells or B cell supernatants, with or without neutralization of B cell-derived IL-10. Functional changes of microglia were assessed by analyzing their ability to activate T cells. B cell regulation was investigated by B cell depletion or adoptive transfer of IL-10-deficient B cells followed by induction of experimental encephalomyelitis (EAE) via MOG peptide using ELISA, FACS and immunohistochemistry.

Results
B cells showed a direct interaction with primary microglia in vitro. Incubation of microglia with IL-10-neutralized B cell supernatant resulted in increased pro-inflammatory cytokine production and an upregulation of co-stimulatory molecules. Functional studies showed that recombinant IL-10 is able to diminish the capacity of microglia to activate T cells as APCs. In vivo depletion of B cells or adoptive transfer of IL-10-deficient B cells worsened clinical severity of EAE and increased the number of CNS infiltrating immune cells. Exacerbation was associated with an enhanced activation and expression of molecules involved in antigen-presentation on microglia.

Conclusion
These findings highlight that B cells substantially alter the functional status of microglia in chronic CNS inflammation. Specifically, B cell-derived IL-10 is capable of diminishing the inflammatory responses of microglia. Our observation suggests that regulatory B cell function may be important in controlling CNS intrinsic inflammation associated with clinical progression.