Cross-talk between Multiple Sclerosis (MS)-relevant B cell subsets and myeloid cells: potential contribution to the CNS-compartmentalized inflammation associated with disease progression
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Objective:
To assess potential cross-talk between multiple sclerosis (MS)-implicated B cell subsets and microglia/macrophage.

Background:
The subpial cortical injury of MS (involving demyelination, neuronal loss and microglial activation) is now thought to represent an important substrate of progressive disease pathology. Of growing interest is the possibility that meningeal inflammation (particularly B cells) contribute to this injury through soluble-factor release. We previously reported that MS patients harbor abnormally increased pro-inflammatory B cells (Beff) which, in the periphery of patients, appear to foster pro-inflammatory responses of circulating myeloid cells. Here we considered whether bidirectional interactions between B cells and resident microglia (and/or infiltrating macrophage) could contribute to propagating CNS-compartmentalized inflammation and injury.

Design/Methods:
Survival and activation of human B cells were assessed (flow cytometry) following in vitro exposure to conditioned-media of pro-inflammatory (M1) or anti-inflammatory (M2a&M2c) human-derived microglia and macrophage. In turn, microglia and macrophage were exposed to soluble products of Beff or regulatory (Breg) B cells, isolated (Miltenyi MACS) from MS patients and matching healthy controls (HC); myeloid cell cytokine secretion (ELISA), phenotype and phagocytic capacity (flow cytometry) were subsequently assessed.

Results:
M1 microglia and macrophage supernatants substantially induced B-cell expression of CD86 and CD95 (n=9; both p<0.0001), while M2c products mediated B-cell death (n=7, p<0.0001). In turn, Beff supernatants increased microglia/macrophage expression of CD80 (n=4-5, p=0.07/p=0.02) and the pro-inflammatory cytokine IL-12, IL-6 and TNF (n=6, p=0.03, p=0.01, p=0.0012 respectively for microglia; n=3-6, p=0.0004, p=0.01, p=0.002 respectively for macrophage), while down-regulating their IL-10 production (n=6, p=0.0024 microglia; n=3-6; p=0.002 macrophage). Breg supernatants enhanced microglia/macrophage expression of TREM-2 (n=4-5, p=0.03/p=0.03). Beff supernatants inhibited, while Breg supernatants induced microglia/macrophage phagocytic function (n=4-6, p=0.01/p=0.03).

Conclusions:
Bidirectional cross-talk between MS-relevant B cell subsets and microglia/macrophage may sustain ongoing cascades of CNS-compartmentalized inflammation and injury, potentially offering new therapeutic targets for future development in progressive MS.