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(Re)solving MS: understand and exploit endogenous protection systems

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Chronic neuro-inflammation is a key pathological hallmark of multiple sclerosis (MS) and suggests that the natural process to resolve inflammation, orchestrated by specialized pro-resolving mediators (SPMs), is dysregulated. By using targeted-metabololipidomics profiling of human cerebrospinal fluid (CSF), we identified unique lipid mediator signatures associated with MS clinical forms and provided first evidence for an altered resolution-inflammation pathway in the CNS of MS patients. In particular, we observed a reduction of SPMs e.g. LXB_4 and RvD3 in specific clinical stages and we identified choroid plexus (CP) epithelial cells as a source of SPMs; when isolated from post-mortem brains of MS patients, these cells showed defects in SPM biosynthesis. SPM treatment of key pathogenic cells in MS, e.g. human microglia and Th1/Th17 lymphocytes, or of experimental autoimmune encephalomyelitis mice reduced their inflammatory response and attenuated disease severity in vivo. Overall, we provide critical evidence of a failed CNS-resolution pathway in MS, suggesting new insights into the pathogenesis and providing innovative diagnostic and therapeutic approaches.

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