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5-LOX ACTIVATING PROTEIN (FLAP): A NOVEL TARGET TO BOOST THE RESOLUTION OF NEURO-INFLAMMATION IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a devastating neurological disease and one of the most prevalent autoimmune disorders in the Western world. Phagocytes, like macrophages and microglia, play a dual role in lesion progression by promoting both inflammation and remyelination. The resolution of inflammation is regulated by bioactive lipid mediators (LMs), which are synthesized by enzymes such as lipoxygenases (LOX) and cyclooxygenases. We observed that 5-LOX expression is present in all central nervous system cell types, but interestingly, 5-LOX activating protein (FLAP) is increased locally in active MS lesions and is mostly confined to microglia. This suggests that activation of the 5-LOX pathway through FLAP under inflammatory conditions is responsible for a detrimental LM shift causing impairment of resolution and enhancing lesion progression. Here, we found that pharmacological inhibition of FLAP halts myelin-induced foam cell formation and reduces proinflammatory cytokine production in LPS-activated microglia *in vitro*. In line with these results, we show that FLAP inhibition reduces the disease score in the *in vivo* experimental autoimmune encephalomyelitis model of MS, both in a prophylactic and therapeutic setting. Furthermore, myelin repair was increased upon FLAP inhibition in the *ex vivo* cerebellar brain slice and *in vivo* cuprizone model of de- and remyelination. Altogether, our results identify FLAP as a novel target to restore the LM balance, thereby preventing neuro-inflammation and promoting repair in MS and other neurological disorders characterized by the presence of chronic inflammation and demyelination.