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"IL4 and IL6 induce pro-survival reactivity and ALOX12 activation in human astrocytes."

Parkinson's Disease (PD) hallmark is the death of dopaminergic (DA) neurons in the Substantia nigra pars compacta (SNpc), a structure of the midbrain that is crucial for modulating the initiation of motor movement, among other specific cognitive and emotion processing functions. Astrocytes, major players in energetic neuronal support, synaptic maintenance as well as in ion and neurotransmitter homeostasis, contribute to the etiology of PD either by gain of toxic function or loss of survival support for the DA neurons. There is an inflammatory component in the PD pathology, with activation of microglial cells and astrocytes noticed in postmortem brains. Maresin 1 (Mar1), a bioactive lipid and derivative of Docosahexaenoic acid (DHA), is a signaling molecule that has been shown to exert its anti-inflammatory function on reactive microglial cells. Mar1 is synthesized by ALOX12, an enzyme expressed in astrocytes, neurons, and microglia. We hypothesized that astrocytes up-regulate and release Maresin-1 in response to certain cytokines to promote homeostasis. To test this hypothesis we exposed rat astrocytes in culture to cytokines (TNFα, IFNγ) in the presence or absence of Maresin-1 and recorded the nuclear translocation of NFkB/p65, a pro-inflammatory transcription factor; we measured the expression of markers of HMGB1, a stress marker, and IL6 and the activity of ALOX12, an enzyme in the synthetic pathway of Mar-1 in the presence of two interleukins 4 and 6, that were proposed to activate biosynthesis of other pro-survival factors in astrocytes. We found that TNFα and IFNγ induced the activation of NFkB/p65 and Mar-1 prevented the transcription factor nuclear translocation. In addition, IL4 increased the transcription of IL6 which induced the activation of ALOX12, leading to elevated production of 14-HDHA and 12-HETE from DHA and Arachidonic acid, respectively. These results suggest that IL6 is a cue that induces survival reactivity by activating the secretion of Mar-1 which promotes anti-inflammatory effects in astrocytes. In future studies, we will determine the mechanisms by which IL6 induce activation of ALOX12 and if that counteracts the inflammatory effects of TNFα and INFγ.

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