N-ACETYLSEROTONIN EXERTS NEUROPROTECTIVE EFFECTS ENHANCING IDO1 CATALYTIC ACTIVITY

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Introduction: Indoleamine 2,3-dioxygenase 1 (IDO1) is a Tryptophan (Trp) degrading enzyme which catalyzes the first and rate-limiting step in the kynurenine pathway, leading to Trp depletion and the production of a series of immunoregulatory molecules collectively known as kynurenines. Both effects are involved in the anti-inflammatory and immunoregulatory action of the enzyme by virtue of which it may represent a major therapeutic target in several autoimmune diseases, including multiple sclerosis (MS). The alternative degradation of Trp occurring along the serotonin pathway yields to N-acetylserotonin (NAS), a metabolite endowed with antioxidant and thus neuroprotective functions in the experimental mouse model of MS. The aim of the study was to investigate whether a correlation exists between NAS neuroprotective effects and IDO1 immunomodulatory activity.

Materials and methods: Conventional dendritic cells (cDCs; the main antigen presenting cells of the immune system) were stimulated with NAS to asses IDO1 expression and activity. WT and Ido1$^{-/-}$ mice were immunized with the myelin oligodendrocyte glycoprotein (MOG) peptide to induce the experimental autoimmune encephalomyelitis (EAE; an animal model of MS) and treated with NAS to evaluate the protective effect of this metabolite.

Results: We found that NAS does not modulate IDO1 expression at both transcript and protein levels, but significantly increases Kyn production in cDCs, suggesting that it acts as catalytic enhancer of IDO1. Moreover, by means of a delayed-type hypersensitivity assay we demonstrated that NAS confers an immunosuppressive phenotype on cDCs, an effect that requires IDO1 activity. We finally found that the protective property of NAS in EAE relies on IDO1 as it is lost in Ido1$^{-/-}$ mice.

Discussion and conclusion: Overall, our data prove that NAS is endowed with immunoregulatory properties acting as catalytic enhancer of IDO1 both in vitro and in vivo.