

Distinct Modulation of Human Myeloid and Plasmacytoid Dendritic Cells by Anandamide in Multiple Sclerosis

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Objective: The immunopathogenesis of multiple sclerosis (MS) has always been thought to be driven by chronically activated and autoreactive Th-1 and Th-17 cells. Recently, dendritic cells (DCs) have also been thought to significantly contribute to antigenic spread and to maturation of adaptive immunity, and have been linked with disease progression and exacerbation. However, the role of DCs in MS pathogenesis remains poorly understood.

Methods: We compared the level of cytokine production by myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in healthy subjects and MS patients, following in vitro stimulation of Toll-like receptors 7/8. We also evaluated the effect of the main endocannabinoid, anandamide (AEA), in these DC subsets and correlated cytokine levels with defects in the endocannabinoid system.

Results: mDCs obtained from MS patients produce higher levels of interleukin-12 and interleukin-6, whereas pDCs account for lower levels of interferon- α compared to healthy subjects. AEA significantly inhibited cytokine production from healthy mDCs and pDCs, as well as their ability to induce Th-1 and Th-17 lineages. Moreover, we found that in MS only pDCs lack responsiveness to cytokine inhibition induced by AEA. Consistently, this specific cell subset expresses higher levels of the anandamide hydrolase fatty acid amide hydrolase (FAAH).

Interpretation: Our data disclose a distinct immunomodulatory effect of AEA in mDCs and pDCs from MS patients, which may reflect an alteration of the expression of FAAH, thus forming the basis for the rational design of new endocannabinoid-based immunotherapeutic agents targeting a specific cell subset.