Selective CB2 receptor activation drives Th0 differentiation towards a Th2 and T regulatory phenotype

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Cannabinoids from Cannabis possess anti-inflammatory and immunomodulatory properties, but the mechanisms responsible for these actions still haven't been unraveled. CB2 is the cannabinoid receptor expressed primarily on hematopoietic cells and mediates the immunoregulatory functions of cannabinoids. Here we used a classical *in vitro* assay for Th lineage specific differentiation of naïve CD4+ T lymphocytes from mouse spleens to study any potential ability of two CB2 selective compounds in the differentiation of T lymphocytes. Th1, Th2, Th9, Th17 and Treg cells were differentiate in the presence of two selective synthetic cannabinoids, CB65 and JTE907, for 6 days and analysed. CB65 and JTE907, a selective agonist and a highly selective inverse agonist, respectively, were both able to differentiate Th0 cells or potentiate the polarized Th2 cells towards the Th2 phenotype. They were able as well to differentiate the Th0 cells towards the Treg phenotype but not to potentiate the Treg polarized cells. Conversely, both cannabinoids counteracted *in vitro*-induced polarization of Th1 cells and didn't have any effect on Th9 and Th17 polarization. Intracellular signals induced by CB65 and JTE907 in Th2 and Treg-oriented polarization were found to be the activation of p38, which peaks at 48h from the start of cell activation, and the activation of STAT5A transcription factor, both involved in the activation of GATA3 (Th2 specific) and Foxp3 (Treg specific) transcription factors. Thus, both p38 and STA5A are activated by CB65 and JTE907, linking the activation of CB2 receptor to the specific transcription factors of Th2 and Treg polarization. Collectively these results indicate that signals through CB2 receptor can drive the immune response towards a specific T cell phenotype thus allowing the use of selective specific ligands as potential therapeutic agents in Th-specific mediated diseases.