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

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Cannabinoids, the Cannabis constituents, are known to possess anti-inflammatory and immunomodulatory properties but the mechanisms involved are not understood. CB2 is the cannabinoid receptor expressed primarily on hematopoietic cells and mediates the immunoregulatory functions of cannabinoids. Here we used an in vitro system of Th lineage specific differentiation of naïve CD4+ T lymphocytes isolated from mouse spleen to study whether the CB2-induced signal could play any role in the polarization of Th0 cells versus Th2, T regulatory (Treg) and Th1 lineages. Results indicate that cannabinoids were able to differentiate Th0 cells untreated or cultured under polarizing conditions. In particular, we showed that CB65 and JTE907, a selective agonist and a highly selective inverse agonist, respectively, of CB2 receptor, induced *in vitro* differentiation of mouse Th0 lymphocytes towards the Th2 lineage and potentiated the Th2 polarized phenotype. CB65 and JTE907 were even able to differentiate Th0 cells towards a T regulatory lineage (Treg) but not to potentiate the Treg polarized phenotype. Conversely, both cannabinoids counteracted in vitro-induced polarization of Th1 cells. 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.