SUMMARY OF RESEARCH_OSCAR PALOMARES, PhD

Cannabinoids induce functional Tregs by promoting tolerogenic DCs via autophagy and metabolic reprograming.

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ABSTRACT:

The generation of functional regulatory T cells (Tregs) is essential to keep tissue homeostasis and restore healthy immune responses in many biological and inflammatory contexts. Cannabinoids have been pointed out as potential therapeutic tools for several diseases. Dendritic cells (DCs) express the endocannabinoid system, including the cannabinoid receptors CB1 and CB2. However, how cannabinoids might regulate functional properties of DCs is not completely understood. We uncover that the triggering of cannabinoid receptors promote human tolerogenic DCs that are able to prime functional FOXP3+ Tregs in the context of different inflammatory diseases. Mechanistically, cannabinoids imprint tolerogenicity in human DCs by inhibiting NF-κB, MAPK and mTOR signalling pathways while inducing AMPK and functional autophagy flux via CB1- and PPARα-mediated activation, which drives metabolic rewiring towards increased mitochondrial activity and oxidative phosphorylation. Cannabinoids exhibit in vivo protective and anti-inflammatory effects in LPS-induced sepsis and also promote the generation of FOXP3+ Tregs. In addition, immediate anaphylactic reactions are decreased in peanut allergic mice and the generation of allergen-specific FOXP3+ Tregs are promoted, demonstrating that these immunomodulatory effects take place in both type 1- and type 2-mediated inflammatory diseases. Our findings might open new avenues for novel cannabinoid-based interventions in different inflammatory and immune-mediated diseases.

DETAILED DESCRIPTION OF THE STUDY:

The generation and maintenance of functional regulatory T cells (Tregs) is indispensable to keep tissue homeostasis and healthy immune responses in many biological contexts and inflammatory diseases such as skin diseases, autoimmunity, metabolic inflammation, pregnancy, cancer, tissue injury, host-commensal interactions,

transplantation, acute and chronic infection or allergy. Different preclinical and clinical studies pointed out cannabinoids as potential therapeutic tools in cancer, neurological and inflammatory diseases. Human and mouse dendritic cells (DCs) express the endocannabinoid system, including the cannabinoid receptors CB1 and CB2. However, how cannabinoids might regulate functions of DCs and their ability to prime Tregs is not yet completely understood.

In this study, we uncover unprecedented molecular mechanisms by which the triggering of cannabinoid receptors promotes tolerogenic DCs able to prime functional FOXP3$^+$ Tregs in the context of inflammatory diseases such as LPS-induced sepsis or food allergy. Under inflammatory conditions, cannabinoids imprint tolerogenicity in human DCs by inhibiting NF-κB, MAPK and mTOR signalling pathways while inducing AMPK and functional autophagy via CB1- and PPARα-mediated activation. Subsequently, autophagy drives metabolic rewiring that shifts glucose metabolism from glycolysis and Warburg effect towards increased mitochondrial activity and oxidative phosphorylation, promoting the generation of human tolerogenic DCs able to polarize functional FOXP3$^+$ Tregs. Remarkably, cannabinoids exhibit *in vivo* protective and anti-inflammatory effects in LPS-induced sepsis by mechanisms depending on CB1- and PPARα-mediated autophagy induction and also promotes the generation of FOXP3$^+$ Tregs. In addition, immediate anaphylactic reactions are decreased in peanut allergic mice and the generation of allergen-specific FOXP3$^+$ Tregs are promoted. These data demonstrate the immunomodulatory effects of cannabinoids in both type 1- and type 2-mediated inflammatory diseases.

Our findings might well contribute to open future avenues for the development of novel cannabinoid-based interventions for different inflammatory and immune-mediated diseases.

We are confident that the novel mechanistic insights on how cannabinoids imprint tolerogenic DCs able to prime functional Tregs and the two preclinical *in vivo* models demonstrating this immunomodulatory capacity in both type 1- and type 2-mediated inflammatory diseases described in this study are of great interest for a broad range of basic researchers and dermatologist and also physicians from a broad range of specialities, as it comprises fundamental basic research with indubitable potential clinical application.