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Cannabidiol Induces Immunomodulation by the Enhancing and Activation of CB2 Receptor Reducing Murine aGVHD

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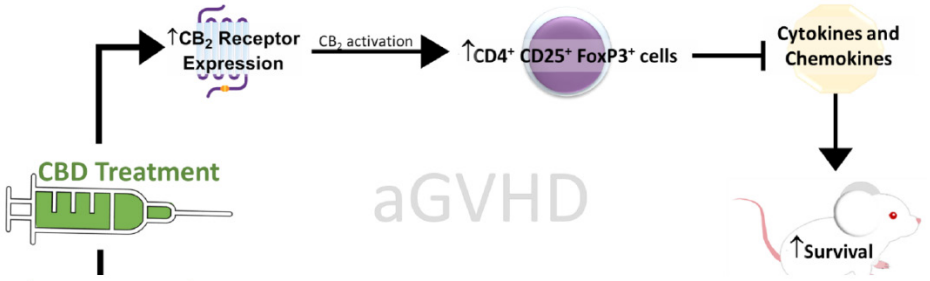
Abstract

CBD treatment, through CB2 activation, increases Tregs in the intestine and reduces cytokine/chemokine release the treatment also increases CD8+ cells maintaining the GVL effect. Altogether, these factors contribute to the protection of target organs and increase in host survival.



Keywords: Hematopoietic stem cells; Cannabidiol; Immunomodulation; Graft-versus-host disease

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Introduction

Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) is a transplant of hematopoietic stem cells between two genetically non-identical individuals [1,2]. It is a curative therapy for several malignant and nonmalignant diseases [3]. The main limitation of this therapy is Graft-Versus-Host Disease (GVHD), an alloHSCT complication, characterized by systemic inflammation and damage in several target organs, manly gut, liver, lung, and skin [3,4]. The immune incompatibilities between donor and host are identified by donor T cells, that react against host tissues, causing extensive damage and high mortality rates, up to 50% [5,6]. On the other hand, as a therapy against malignant diseases, alloHSCT provides a stronger Graft-Versus-Tumor (GVT) reactivity, promoting the identification and eradication of reminiscent tumor cells [7,8]. Therefore, the ideal management of GVHD would be the modulation of the immune response without interfering in GVT effect.

Our team has investigated several approaches in GVHD treatment through the years, focused on inflammatory response in the target organs. In this sense, the cannabinoid system has appeared as a very complex, but interesting, approach to immunomodulation. Cannabidiol (CBD) is a non-psychoactive drug with well-described anti-inflammatory properties and is currently in a Phase II study for the treatment of GVHD [9]. Thus, our goal was to better comprehend the effects and mechanisms of CBD treatment in the target organs inflammation of mice submitted to GVHD.

Murine Model of Acute GVHD (aGVHD)

In a murine model of acute GVHD (aGVHD), with allogeneic transfer from C57BL6/J to Balb/c, after total body irradiation [10], daily treatment with CBD did not interfere in the bone marrow engraftment process. This was verified in the bone marrow itself and in the spleen, seven days after the transplantation procedure. The presence of transplanted cells in host secondary lymphoid organs is highly important to preserve immune response and also the reactivity against reminiscent malignant cells; however, it is also related to the development of aGVHD [11]. Therefore, CBD was not only responsible for an increase in survival but also maintained GVT reactivity. These results are of utmost importance when considering any drug as a candidate for either prevention or treatment for GVHD.

CBD also protected intestinal barriers and preventing bacterial migration into the peritoneal cavity. Generally, in GVHD, due to intestinal damage, the intestinal barrier is inefficient in preventing bacterial translocation, and, therefore, bacteria are found in the peritoneal cavity. Presence of indigenous gut bacteria in the peritoneal cavity can leads to local and systemic inflammation, sepsis, and a worse prognosis of GVHD patients [12,13]. Regarding cell migration and adhesion, CBD treatment did not reduce this process. Unlike, treatment with CBD increases the percentage of T CD4+ or T CD8+ cells in intestine, without increasing their activation status. In the T CD4+ profile there was an increase in T regulatory cells. This could explain the reduction of intestinal damage and may also contribute to the reduction in both cytokines (TNF-a and IFN-g) and chemokines (CCL2, CCL3, and CCL5) levels (Figure 1). It is interesting to highlight that these chemokines are mandatory for cellular recruitment during inflammatory processes in target organs [14-16].

In the liver, another important target organ, CBD treatment promoted a decrease in CCL2, CCL3, and IFN-γ levels and thus protection against damage. Furthermore, CBD promoted an increase in the number of lymphocytes in the liver, mainly in CD4+ populations. Although there was no increase in Treg cells, but CD4+ cells were found to be more activated. These findings and the work of Panoskaltsis-Mortari, Price [17], suggesting that not only the inflammatory process is delayed, when comparing liver and intestine, but also CD4+ cells differentiation into FoxP3+ cells would occur later in the liver.

An interesting part of CBDs mechanism in our model was that Cannabinoid Receptor 2 (CB2), but not Cannabinoid Receptor 1 (CB1) is partially responsible for mice survival, and it is our belief that it may also be responsible for CBD immunomodulatory effects. Furthermore, the CB2 receptor is present in immune cells and its activation is correlated to cytokine inhibition [18,19]. CBD induced an increase in CB2 receptor expression in the intestines of mice subjected to aGVHD and this receptor was found to be co localized with CD4 and FoxP3 cells in the intestine. Altogether, these findings reinforce the role of CB2 in immune modulation and that cannabidiol might stimulate FoxP3 differentiation by interaction with CB2 receptor. Additionally, the presence of Tregs is necessary for the promotion of immune tolerance, preventing an overwhelming graft immune response after alloHSCT [20-22].

Conclusion

The effects of cannabidiol are associated with CB2 activation but it is important to highlight that, this highly lipidic phytocannabinoid can also interact with several other receptors and additional mechanisms may underlie the full modulatory effects of CBD. In our model of aGVHD, this treatment promoted an increase in survival and prevented damage to target organs. The increase in CB2 receptor expression in the intestine provides an immunoregulatory environment with the reduction of major aGVHD pro-inflammatory mediators. However, CBD also promotes an increase in the number of CD8+ cells, maintaining the GVT effect. Therefore, CBD represents an interesting approach to be further evaluated in the treatment of aGVHD.

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