IDENTIFICATION OF THE MECHANISMS THROUGH WHICH BOTANICALS ATTENUATE PATHOGENESIS OF HUMAN DISEASES

ABSTRACT

Plant products have been used for a long time in treatment of diseases. In fact, more than half of approved medicines are derived from plants or other natural products. Despite the fact that the synthetic drugs are effective in treating many human diseases, there is no cure against several clinical disorders. Moreover, a significant number of diseases can be prevented thereby causing less burden on societal healthcare costs as well as promoting healthy lifestyles. Thus, botanicals offer a unique opportunity to explore novel compounds to prevent and treat various clinical disorders as well as understand their mode of action so that new targeted therapeutics can also be developed.

For that reason, we studied the efficacy of two different natural products in treatment of two diseases models and explored the mechanism behind their therapeutic effects in both diseases. The first one was asthma mouse model treated with resveratrol. Asthma is a chronic inflammatory disease of airways mediated by T-helper lymphocytes (Th2) cells involving complex signaling pathways. Resveratrol, a phytoalexin, has been previously shown to attenuate allergic asthma although the role of miRNA in this process has not been studied. In the current study, we investigated the effect of resveratrol on ovalbumin-induced experimental allergic asthma in mice. To that end, BALB/c mice were immunized with ovalbumin (Ova) intraperitoneally followed by oral gavage of vehicle (Ova-veh) or resveratrol (100 mg/kg body) (Ova-res). On day 7, the experimental groups received intranasal challenge of Ova followed by 7 days of additional oral gavage of vehicle or resveratrol. At day 15, all mice were euthanized and bronchoalveolar fluid (BALF), serum and lung infiltrating cells were collected and
analyzed. The data showed that resveratrol significantly reduced IL-5, IL-13, and TGF-β in the serum and BALF in mice with Ova-induced asthma. Also, we saw a decrease in CD3+CD4+, CD3+CD8+, and CD4+IL-4+ cells in pulmonary inflammatory cell infiltrate in Ova-res group when compared to Ova-veh. MiRNA expression arrays using lung infiltrating cells showed that resveratrol caused significant alterations in miRNA expression, specifically downregulating the expression of miR-34a. Additionally, miR-34a was found to target FOXP3, as evidenced by enhanced expression of FOXP3 in the lung tissue. Also, transfection studies showed that miR-34a inhibitor upregulated FOXP3 expression while miR-34a-mimic downregulated FOXP3 expression. The current study suggests that resveratrol attenuates allergic asthma by downregulating miR-34a that induces increased expression of FOXP3, a master regulator of T-regulatory cells (Treg) development and functions.

The pivotal roles of the microbiota residing along mucosal surfaces, both local and distal to the afflicted site, have garnered an appreciation in the field of immunology when studying autoimmune disorders. In this study we focused on the bioactive molecule resveratrol (RES), a polyphenol compound derived from plants. Resveratrol is known for its multifaceted approach to combat autoimmune disorders via its anti-inflammatory, anti-microbial and anti-oxidative properties. In this study, we focused on the direct effects of resveratrol supplementation on the clinical symptoms of ovalbumin (OVA)-induced murine allergic response, as well as the effects on bacterial composition of the pulmonary tract and the cecum, and on the expression of tight junction-regulating genes in the lung epithelium. We found that resveratrol induced colonization of Akkermansia muciniphila in the lung tissue and Bacteroides acidifaciens in the colon of resveratrol-treated OVA-stimulated mice, relative to VEH-treated mice. In addition, we found that RES induced significant changes in tight junction and PPAR-γ gene expression in
pulmonary epithelium of OVA-stimulated mice treated with RES, when compared to those mice treated with VEH. We conclude that RES has promising efficacy in the treatment of asthma and its effect may be mediated by changes in gut-lung microbiome axis.

The second disease model we studied was neuroblastoma, Neuroblastoma (NBL) is one of the most common childhood cancers that originates from the immature nerve cells of the sympathetic system. Studies with NBL cancers have also shown that miRNAs are dysregulated and may play a critical role in pathogenesis. Cannabidiol (CBD) is a non-psychoactive compound found in marijuana which has been previously shown by our laboratory and others to induce apoptosis in cancer cells. However, there are no studies reported to test if CBD mediates these effects through regulation of miRNA. In the current study, therefore, we investigated if CBD induces apoptosis in human NBL cell lines, SH SY5Y and IMR-32, and if it is regulated by miRNA. Our data demonstrated that CBD induces apoptosis in NBL cells through activation of serotonin and vanilloid receptors. We also found that caspase-2 and -3 played an important role in the induction of apoptosis. CBD also significantly reduced NBL cell migration and invasion in vitro. Furthermore, CBD blocked mitochondrial respiration and caused a shift in metabolism towards glycolysis. CBD altered the expression of miRNA specifically, down-regulating hsa-let-7a and upregulating hsa-mir-1972. Downregulation of let-7a increased expression of target caspase-3, and growth arrest specific-7 (GAS-7) genes. Upregulation of hsa-mir-1972 caused decreased expression of BCL2L1 and BCL2 genes. Together, our studies suggest that CBD-mediated apoptosis in NBL cells is regulated by miRNA.
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