MASTER'S THESIS

Traditional Chinese Medicine Modulate Antigen Processing in Dendritic Cell-Mediated T Cell Response in Parkinson's Disease and Gut Microbiota Composition in Irritable Bowel Syndrome

NG, Lam

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ABSTRACT

Part A

Traditional Chinese Medicine Modulates Antigen Processing in Dendritic Cell-Mediated T Cell Responses in Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disease that affects the elderly. It is associated with motor dysfunction due to the accumulation of misfolded or aggregated fibrillar alpha-synuclein (α-syn) in the mid-brain. Current treatments mainly focus on relieving the symptoms but are accompanied by side effects and are limited in halting disease progression. Increasing evidence points to peripheral immune cells underlying disease development, especially T cells contributing to α-syn-related neuroinflammation in PD. The onset of these T cell responses is likely mediated by dendritic cells (DCs), but their roles in α-syn-specific responses remain less studied. Moreover, traditional Chinese medicine (TCM) derived compounds that are candidates to treat PD may alleviate DC-T cell mediated immune responses. Therefore, in our study, we focused on the roles of DC in response to fibrillar α-syn and subsequent induction of inflammatory and T cell responses. Monomeric α-syn was used as a comparison to highlight the differences between physoplogical and disease conditions. The effects of TCM Curcumin-derived C1, and *Tripterygium wilfordii* Hook F-derived Celastrol in mediating DC-T activities will also be examined. We found that although fibrillar α-syn did not induce significant inflammatory or T cell-mediating cytokines, robust pro-inflammatory T cell responses were found by co-culturing fibrillar α-syn-pulsed MoDCs with α-syn-specific $CD4^+$ T cells. Celastrol, but not C1, reduced the onset of pro-inflammatory T cell differentiation, by promoting endo-lysosomal, amphisomal and autophagic vesicles interacting with fibrillar α-syn, which likely lead to its degradation and thus fewer antigen peptides available for T cell recognition. Comparatively, monomeric α-syn can be processed effectively through endo-lysosomal and autophagic pathways with less assistance from Celastrol. In conclusion, regulating the intracellular trafficking and processing of α-syn by DCs can be a potential approach to control the progression of PD, in which Celastrol can be a candidate to accomplish this.

Part B

Traditional Chinese Medicine Modulates Gut Microbiota Composition in Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder (FGID) diagnosed by abdominal pain and changes in bowel habits that happen at least one day per week for a consecutive six months. The multifactorial pathophysiology of IBS renders it challenging to identify a specific pathological hallmark, and it usually involves malfunctioning of multiple biological systems. Gut microbiota has long been highlighted as one of the contributing factors in IBS development and progression. Alterations in gut microbiota adversely affect the gut environment and activities, including defecation, digestion, and immunity, which could negatively impact the brain's cognitive and emotional functions and affect patients' quality of life. Current treatments mainly aim to relieve IBS symptoms through modulating gut microbiota, diet and maintaining mental stability. However, the therapeutical outcomes vary among individuals due to the lack of understanding of individual-to-individual variations in gut microbiota remodelling towards different interventions. Therefore, the establishment of a network-based computational method that can be used to study gut microbiota composition, metabolic products, and the complex relationship among individual microbe in the whole microbial community would bring advantages to the prediction of treatment outcomes and allow a better understanding of the dynamics of gut microbiota in relations to IBS. Herein, we used a Chinese herbal formula, JCM-16021, as an intervention agent on the IBS-like rat model established by neonatal maternal separation (NMS). Defecation frequency, faecal water content, visceral pain sensitivity, and total faecal bacterial loads were measured to study the therapeutical effect of JCM-16021 with regards to the modulation of microbiota composition. We found promising symptom improvements in JCM-16021 treated rats, while the detailed study of microbiota under JCM-16021 treatment will be further determined through metagenomics, metabolomics and nanopore sequencing. It is expected that the JCM-16021 promotes a change of microbial composition which resembles that of the healthy controls or an increase of microbial groups that are important in maintaining typical gut environment and activities.