Intestinal bacteria in treatment of behcet’s disease (bd)

The hypothesis

We propose that certain intestinal bacteria have potential roles in the treatment of uveitis patients with Behcet's disease (BD) through the modulation of Th17 cells.

Introduction of Behcet's disease

BD is a systemic inflammatory disease of unknown origin that has a diverse spectrum of clinical manifestations, including mucocutaneous, vascular, gastrointestinal, musculoskeletal, and central nervous system involvement. The prevalence of BD is higher along the Silk Road than other areas. HLA B51 is considered a genetic risk factor. The prevalence of this allele is around 20% in the general population along the Silk Road and 50–80% among BD patients. However, it's only 2–8% in the general population and 15% among BD patients in Northern Europe and the US [1]. BD is seldom seen in childhood and has an equal frequency in males and females. Treatment includes corticosteroids and other immunosuppressive agents, such as anti-tumor necrosis factor, interferon-α.

Th17 cells participates in the pathogenesis of Behcet's disease

Nowadays, there are several hypotheses to explain the pathogenesis of BD, among which a new subset of T helper cells, Th17 cells gained increasing attention. Th17 cells mainly produce IL-17, IL-22, TNF-α and are involved in neutrophilia and organ specific autoimmunity. IL23 is one of the main Th17 pathway activator, which can induce IL-17 production [2]. Genome-wide association studies (GWAS) identified IL23R-IL12RB2 as BD susceptibility loci [3, 4], which suggested that Th17 cells participate in the development of this disease. In active BD patients with central nervous system involvement ,

Th17 cells were found in the CSF, brain parenchyma and intracerebral blood vessels[1]. Investigations have found that IL-17 was elevated in active BD patients as compared to inactive BD or controls [5, 6]. Th17/Th1 ratio was elevated in BD patients as compared to controls [7]. Sera from BD patients were able to induce Th17 differentiation of CD4+ T cells from healthy controls [1]. All these results above indicated the important role of Th17 and IL-17 in the pathogenesis of BD.

Th17 cells are also important in the development of BD patients with uveitis

Ocular involvement is observed in half of BD patients. Bilateral eye involvement is always seen and is characterized by a nongranulomatous uveitis and retinal vasculitis. Patients often endure recurrent attacks and spontaneous resolution. Male patients have more severe disease course, and have higher risk of vision loss. Experiments have also shown that Th17 cells participate in the pathogenesis of uveitis caused by BD. In BD patients with active uveitis, both the total amount of Th17 cells and the frequencies ofthem from peripheral blood mononuclear cells (PBMCs) were significantly upregulated[8, 9].

Human intestinal microbiota play critical roles in the immune system

The human intestinal lumen contains 1011 bacteria per gram of contents, which are called microbiota. They mainly contains four phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria[10]. The intestinal microbiota perform numerous functions, including digestion, defense against pathogens, and modulation of the immune system[11]. The mucosal associated immune system contains about 80% of the immunologically active cells of the human body, most of which are present in the intestine.

Thus, there are complex interactions between the immune cells, neurons and the microbiota in the intestine.

Experiments using germ-free animals showed many morphological and physiological intestinal tissue defects during the development, including surface barrier[12]. It is well known that the intestinal surface barrier is one of the most important components of the immune system. Intact surface barrier can separate immunogenic agents from immunoreactive submucosa, thus prevent undesired immune reaction and the subsequent autoimmune diseases [13, 14]. For example, in type 1 diabetes[15] and Hashimoto’s thyroiditis, morphological changes in intestinal epithelial cells and intraepithelial lymphocyte infiltration have been found [16]. Patients with type 1 diabetes[17, 18], multiple sclerosis[19, 20], or rheumatoid arthritis[21] were demonstrated to have increased intestinal permeability[22-25]. Under such circumstances, both antigens from environmental and intestinal microbiota will easily get into the circulation and induce systemic or organ specific immune responses. Antibiotics could relive symptoms of some kind of autoimmune diseases, such as rheumatoid arthritis, Crohn’s disease and multiple sclerosis [26, 27]. Change intestinal microbiota of experimental animals through using of antibiotics or transferring them into a germ-free environment can result in either exacerbation or reduction in autoimmune disease manifestation. These findings suggested that the intestinal microbiota participate in the pathogenesis of autoimmune diseases.

Intestinal microbiota can induce Th17-dependent autoimmune disease

Th17 cells are most abundant in the intestinal lamina propria, they have critical roles in mucosal defense pathogenesis[28]. Antimicrobial peptides (AMPs), which are produced by intestinal epithelial cells in response to TLR signals, can inhibit pathogens from entering the mucosal barrier and draining lymph nodes [29, 30]. Th17 cells can induce AMPs production through IL-22. Mice deficient for IL-22 or its upstream regulator, IL-23, couldn’t produce AMPs, and were highly susceptible to infection [31]. Their presence in the intestine required colonization of mice with microbiota [32, 33]. In germ-free mice, Th17 cells were absent[34]. Intestinal commensal, segmented filamentous bacteria (SFB) is sufficient to influence Th17 cells in the intestine and, potentially, systemically as well. Experiments had already found that SFB could promote Th17-dependent autoimmune disease in animal models [35, 36]. From these results, we may suspect that those with high levels of intestinal SFB may be predisposed to Th17-mediated autoimmune diseases.

Certain intestinal bacteria can reverse the upregulation of Th17 cells

IL-27 has been found to inhibit the generation of Th17 cells. When simulated with TGF-β and IL-6, the level of IL-17 increased and the level of IL-27 decreased in murine splenocytes. B. longum JCM 1222T could directly inhibit IL-17 production and indirectly through promoting IL-27 production. Another strain, S. thermophilus ST28, could suppress the Th17 cells response in inflamed intestines [37]. Lactobacillus gasseri A5 could also suppress Th17 cells response both in an allergic asthma mouse model and in stimulated splenocytes [38]. These findings implied that certain intestinal bacteria have

immunomodulatory function. In the future, we may use these bacteria to treat Th17-mediated autoimmune diseases.

Testing the hypothesis

Uveitis patients with Behcet disease can be selected and divided to two groups according to the disease activity (active vs. inactive). Normal people with matched age and gender can be used as controls. At baseline, quantitative metagenomics analysis developed by the MetaHIT consortium will be used to construct a gene catalogue. Then this uveitis gene catalogue will be compared with three other gut microbial catalogues: MetaHIT, HMP, and T2D. Then the relative abundances of phylum, class, order, family, genus and species between two uveitis group and control groups were compared. Then certain intestinal bacteria, such as B. longum JCM 1222T will be given to the patients. After the treatment, quantitative metagenomics analysis will be done the second time. The differences between these two quantitative metagenomics analysis will elucidate the role of intestinal microbiota in the pathogenesis of Behcet uveitis.

Consequences of the hypothesis

Since uveitis patients with BD often have recurrent attacks and severe vision impairment, and the immunosuppressive agents have many side effect, it is urgent to find a more effective and safer treatment option. Studies to test our hypothesis will generate new knowledge about the immunomodulatory effects of intestinal microbiota in the uveitis patients with BD. The application of certain intestinal bacteria might be a new therapeutic approach for uveitis patients with BD.