PROBIOTICS FOR HYPER-IMMUNE DISORDERS: SELECTION AND MODE-OF-ACTION

Im S.
Institute for Basic Science (IBS) and POSTECH, Republic of Korea

Introduction:
Alteration of gut microbiota composition is associated with diverse immune disorders and restoration of dysbiosis in disease state with beneficial microorganism could confer the health benefits. As a modulator for dysbiosis Daily intake of oral probiotic preparations has been widely considered. Probiotics are nonpathogenic live microorganism that can provide a diverse health benefits on the host. Recently, many reports suggest that certain probiotic strains or mixture of them could exert potent immunomodulatory activity in diverse disorders. However, efficacy of probiotics is quite different depending on the type of strains and the amounts of doses. Definition of beneficial microorganisms (including probiotics) should be different depending on the types of diseases and health condition of individual person. In our lab, we have been interested in developing probiotics that could suppressing hyper-immune disorders or enhancing immune system, and has developed diverse ex vivo and in vivo screening and evaluation systems.

Methods:
To selectively identify probiotic strains that could enhance the generation of CD4+Foxp3+ regulatory T cells (Tregs), we have developed ex vivo screening systems. Mesenteric lymph node cells or whole splenocytes were co-cultured candidate probiotic strains for 72 hours and then the levels of anti-inflammatory (IL-10), pro-inflammatory (IL-12) or Treg (Foxp3+) markers were analyzed by ELISA and flow cytometry. Probiotic strains with IL-10highIL-12low Foxp3high inducing property were selected and combined to evaluate their immunoregulatory effect on hyper-immune disorders such as autoimmunity and allergic disorders.

Results:
Using the system, we identified several probiotic strains and a mixture of probiotics (IRT5) that up-regulates Tregs in vivo. Administration of the IRT5 induced both T-cell and B-cell hyporesponsiveness and down-regulated T helper (Th) 1, Th2, and Th17 cytokines without apoptosis induction. It also induced generation of CD4(+)Foxp3(+) Tregs from the CD4(+)CD25(-) population and increased the suppressor activity of naturally occurring CD4(+)CD25(+) Tregs. Conversion of T cells into Foxp3(+) Tregs is directly mediated by regulatory dendritic cells (rDCs) that express high levels of IL-10, TGF-beta, COX-2, and indoleamine 2,3-dioxygenase. Administration of probiotics had therapeutic or prophylactic effects in experimental disease models of inflammatory bowel disease and in non-mucosal immune disorders such as atopic dermatitis, hapten-induced contact hypersensitivity, rheumatoid arthritis, myasthenia gravis and multiple sclerosis. The immunoregulatory effect of the IRT5 probiotics is associated with enrichment of CD4(+)Foxp3(+) Tregs in the inflamed regions. In addition, monoclonization of Bifidobacterium bifidum IRT in germ free mouse significantly enhanced the generation of induced CD4+Foxp3+Helioslow Treg (iTreg) cells and upregulated CTLA4 expression. Treatment of BMDCs and CD4+ T-cells treated with Bifidobacterium bifidum IRT or capsular polysaccarides from the strain produced high amount of IL-10 in TLR-2 dependent manner. Currently we are investigating the underlying mechanism of iTreg cell generation by elucidating effector molecules from the probiotics.
strains. Collectively, the administration of probiotics that enhance the generation of rDCs and Tregs represents an applicable treatment of inflammatory immune disorders. This study was supported from the Institute for Basic Science (IBS; IBS-R005-G1), Republic of Korea.

**Keywords:** Hyper-Immune Disorders, Enhancing immune system, Atopic dermatitis, Hapten-induced contact hypersensitivity, Rheumatoid arthritis, Myasthenia gravis, Multiple sclerosis, Probiotics

**Citation:**