学位論文内容の要旨

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学位論文題名

Studies on the role of gut microbiota in the regulation of RegIIIβ and RegIIIγ in murine intestine

（マウス小腸のRegⅢβおよびRegⅢγの発現調節における腸内細菌叢の役割に関する研究）

RegIIIβ and RegIIIγ are C-type lectins expressed in the intestinal epithelial cells. These lectins are secreted into the intestinal lumen and exert bactericidal action whereby intestinal infection is prevented. The intestinal expression of RegIIIβ and RegIIIγ is influenced by both gut microbiota and diet. Because consumption of high-fat diet (HFD) and indigestible saccharides including fructooligosaccharide (FOS) alter both the intestinal expression of RegIIIβ and RegIIIγ and the composition of gut microbiota, this study assumed that gut microbiota may mediate diet-induced changes in the intestinal expression of RegIIIβ and RegIIIγ. Therefore, this study tested this idea and investigated underlying molecular mechanism.

1. Role of gut microbiota in dietary regulation of RegIIIβ and RegIIIγ

This study tested whether changes in the intestinal expression of RegIIIβ and RegIIIγ by supplementation with 1-kestose (KES), a kind of FOS, and by consumption of HFD are mediated by gut microbiota. To do this, this study employed fecal microbiota transplantation (FMT); thus, antibiotics-treated mice were received FMT from mice supplemented with and without KES and from mice fed HFD and normal-fat diet (NFD). Intestinal mRNA levels of *Reg3b* and *Reg3g* genes were lower in mice receiving FMT from HFD-fed mice than in those receiving FMT from NFD-fed mice and higher in mice receiving FMT from KES-supplemented mice than in those receiving FMT from mice without KES supplementation. These results suggest that HFD- and KES-induced changes in the intestinal expression of *Reg3b* and *Reg3g* genes are mediated, at least in part, by gut microbiota.

2. Gut microbes regulating intestinal RegIIIβ

This study explored the specific bacteria responsible for intestinal RegIIIβ regulation. Leptin, an adipocyte hormone, signals nutritional status to the central nervous system and peripheral organs. Because leptin status is reportedly associated with the intestinal expression of *Reg3b*, leptin deficient *ob/ob* mice, leptin receptor-deficient *db/db* mice, and wild type (+/+) mice were included in analysis. The composition of gut microbiota in mice supplemented with and without KES, *ob/ob* mice, *db/db* mice, and +/+ mice was analyzed by 16S rRNA gene sequencing. The data showed that the abundance of the family Ruminococcaceae_Incertae_Sedis, family Clostridia_UCG-014, and genus *Alloprevotella* is positively correlated with the intestinal mRNA level of *Reg3b*. Because these bacterial groups contain several butyrate-producing bacteria, this study assumed that butyrate, a fermentation product of gut microbiota, may be a trigger of intestinal expression of *Reg3b* gene.

3. Mechanistic studies on the RegIIIβ regulation using intestinal organoids

Murine intestinal organoids were used as an *ex vivo* model for intestinal epithelium. The mRNA levels of *Reg3b* and *Reg3g* genes were increased by supplementation of butyrate and another fermentation product propionate in the intestinal organoids. Butyrate and propionate regulate the expression of several genes by inhibiting histone deacetylase (HDAC). Supplementation of trichostatin A, an HDAC inhibitor, increased the expression of *Reg3b* and *Reg3g* genes in the organoids, suggesting that butyrate and propionate upregulate the intestinal expression of *Reg3b* and *Reg3g* genes through HDAC inhibition.

Overall, this study presented the crucial role of gut microbiota in diet-induced changes in the intestinal expression of antibacterial peptides, RegIIIβ and RegIIIγ. Mechanistically, this study proposes that butyrate and propionate, fermentation products of gut microbiota, regulate the expression of *Reg3b* and *Reg3g* genes through HDAC inhibition. The present findings therefore shed light on the novel strategy to control the intestinal infectious diseases.