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Mini Review

Gut microbiota and Intestinal Immune systems -Immune control functions via short-chain fatty acids, Amino acid metabolites and Bile acids

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Introduction

Intestinal environments, including gut microbiota, are deeply involved in the developments and control of intestinal immune systems. Gut microbiota exerts various actions on immune cells through bacterial cell components and metabolites produced by the bacteria.

In addition, since some of the metabolites produced by the bacteria use dietary components as substrates, dietary components are also important factors which affect the control of immune functions via gut microbiota. In this review, we will explain the immune control functions of short-chain fatty acids and bile acids, and the immune control functions of intestinal bacteria through amino acid metabolism, with recent findings.

Immune control functions by short-chain fatty acids

Short-chain fatty acids are functional metabolites produced by gut microbiota with 6 or less carbon chains. The main short-chain fatty acids are acetic acid (C2), propionic acid (C3) and fatty acid (C4). These are produced by fermentation by intestinal bacteria using dietary fiber, oligosaccharides, resistant starch which are indigestible carbohydrates, as substrates, and act on G protein-coupled receptors (GPCRs; GPR41, GPR43) expressed in immune cells and in the nucleus. It exerts its immune control functions through histone modification control. For example, acetic acid is produced by Bifidobacterium spp. [1] and exerts anti-inflammatory effects by promoting apoptosis of neutrophils via GPR43 [2]. Propionic acid is produced by Akkermansia muciniphilia, Veillonella spp. and some Bacteroides spp. [3], and fatty acid is produced by Faecalibacterium prausnitzii and Roseburia spp. [4, 5]. Inhibits the activity of deacetylase (HDAC) [6]. As a result, regulatory T cell differentiation and proliferation are induced by inducing the expression of the Foxp3 gene through histone acetylation [7]. Fatty acid also induces differentiation into regulatory T cells in the large intestine via GPR109A expressed on dendritic cells [8]. It has been reported that the action of such short-chain fatty acids improves inflammatory bowel diseases [7, 8]. Moreover, propionic acid promotes the differentiation of dendritic cells and macrophages into progenitor cells in the bone marrow via GPR41 and acts to suppress the expression of MHCII and CD40 in those cells, thereby allergic airway. It has been reported that inflammation is suppressed [9].

In addition to the above-mentioned effects, short-chain fatty acids also play an important role in IgA antibody production in the intestinal tract. It promotes IgA antibody production through induction of aldehyde dehydrogenase 1 family, member A2 (ALDH1a2) expression in dendritic cells [10, 11]. Furthermore, it has been reported that by activating glycolysis in B cells, energy metabolism is enhanced, and differentiation into IgA plasma cells and IgA antibody production are enhanced [12]. As a proof of this effect, it has been reported that in mice orally infected with Citrobacter rodentrium, it promotes the elimination of Citrobacter rodentrium in the intestinal tract and exhibits an infection protective effect [11].

In this way, short-chain fatty acids produced by intestinal bacteria show anti-inflammatory and intestinal IgA antibody production / promoting effects by acting on immune cells, and maintain intestinal homeostasis to protect against the infection by pathogenic bacteria.

Immune control functions through amino acid metabolism by gut microbiota

Amino acids are also converted into metabolites with immunoregulatory function by being metabolized by intestinal bacteria. For example, indole, which is an intestinal bacterial metabolite derived from tryptophan, produces various types of stagnation due to the branching of metabolic pathway intermediates or metabolic pathways. Indol-3-aldehyde (IAld), one of the indole relatives, is produced by the metabolism of indol-3-acetic acid (IAA) produced by Bacteroides and Clostridium by Lactobacillus spp. Produced [13, 14]. It promotes the production of IL-17 and IL-22 via the aryl hydrocarbon receptor (AhR), which is highly expressed in Th17 cells and ILC3 in the intestinal tract, and recruit neutrophils to infected areas and C from intestinal epithelial cells. It has been reported that it acts to protect against infection against pathogens such as Clostridium rodentrium by inducing the secretion of the type Lectin Reg III family [15, 16].

In addition, it has been reported that many Bifidobacterium spp. are present in the feces of lactating infants and produce indol-3-lactec acid (ILA) [17]. ILA is thought to contribute to the maintenance of intestinal homeostasis by suppressing the differentiation into Th2 cells

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and Th17 cells by inducing the expression of galectin-1, which is an immunomodulator in Th2 cells and Th17 cells [17].

In addition, polyamines produced by enterobacteria from arginine have also attracted attention [18]. When putrescine, a type of polyamine, is taken up by colonic macrophages, it is converted to spermidine and induces M2 macrophages to exert anti-inflammatory functions [19].

As described above, metabolites produced by amino acid metabolism by intestinal bacteria act on intestinal immunity to exhibit antibacterial activity and anti-inflammatory activity, and work to protect against infections and maintain intestinal homeostasis.

Immune regulations by bile acids

Bile acids are produced in liver as suture-type primary bile acids, and after being secreted into the duodenum, most of them undergo dehydration conjugation and dihydroxylation reactions by intestinal bacteria to become secondary bile acids, which have various immunoregulatory functions. show. For example, a type of secondary bile acid, 3-oxo-lithocholic acid (3oxo-LCA), binds to the nuclear transcription factor (RORγt) in T cells and inhibits transcriptional activity, thereby suppressing the differentiation of Th17 cells [20]. On the other hand, isoallo-LCA promotes the differentiation of regulatory T cells by inducing Foxp3 expression in T cells through enhanced production of reactive oxygen species (ROS) from mitochondria and the accompanying histone acetylation modification [20]. As described above, secondary bile acids maintain the homeostasis of intestinal immunity by exhibiting different actions depending on the structure.

Besides, bile acids have been reported to regulate the number of natural killer T cells (NKT cells) in liver. CXCL16, a type of chemokine produced from hepatic sinusoidal endothelial cells, has the function of accumulating NKT cells in the liver via CXCR6 and increasing the number [21]. The primary bile acid tauro-β-muricholic acid enhances the expression of the Cxcl16 gene in liver sinusoidal endothelial cells, while the secondary bile acid ω-muricholic acid derived from gut microbiota suppresses the expression of the Cxcl16 gene. [21]. Therefore, administration of antibiotics to mice to eliminate gut microbiota attenuates the signal from ω-muricholic acid, resulting in an increase in NKT cells in liver [21].

As described above, bile acids whose structural balance is controlled by intestinal bacteria exhibit various immunoregulatory functions such as regulation of differentiation of Th17 cells and regulatory T cells in the intestinal tract and regulation of NKT cells in liver.

Conclusions and Prospections

This time, we focused on short-chain fatty acids, amino acid metabolites and bile acids to explain the intestinal bacteria and intestinal immune system. However, there are various unsolved problems with gut bacteria and the intestinal immune system. For example, the problem of enhancing IgA production by the coordinated action of gut microbiota-dependent IgA-producing proliferating cells [22] and adipose metabolites [23], the function produced by the action of gut microbiota and long-chain fatty acids. It is a unique immunoregulatory function of sex fatty acid metabolites [24,25,26,27] and Alikanegenes, a symbiotic bacterium in Payer plate tissues [28].

Regarding intestinal bacteria and the intestinal immune systems, these issues must be clarified in the future.

Due to dramatic developments of intestinal bacterial research in recent years, metabolites produced by each intestinal bacterium using dietary components as substrates have been identified one after another, and the receptors, expressing cells, and immunological phenotypes of each metabolite have also been elucidated. However, there are individual differences in the intestinal flora and eating habits, and it is expected that different metabolites will be produced for each individual.

Therefore, when considering the immunoregulatory functions of metabolites derived from intestinal bacteria, it is important to consider the composition and function of the intestinal flora of an individual. If this information is aggregated, individualized and stratified treatment should become possible. The results of future research are awaited.

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