

Review

## Effects of Interactions Between Intestinal Microbiota and Intestinal Macrophages on Health

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**Abstract.** *Macrophages reside in every tissue of the body and play an important role in maintaining homeostasis. The intestinal mucosa is the largest immune organ and harbors macrophages in abundance. Dysfunction of intestinal macrophages is characteristic of patients with certain inflammatory bowel diseases. Although intestinal macrophages exhibit hyporesponsiveness to foreign substances, including various bacterial products, their physiological functions are unknown, but may be related to the contribution of intestinal bacteria to the maintenance of various physiological functions of the host. Moreover, recent reports suggest that there are associations between intestinal microbiota and the onset of pathologies, such as diverse metabolic syndromes, depression, and cancer. Evidence indicates that the host's immune response to intestinal microbiota may be etiologically-linked to these diseases; however, the mechanisms are poorly understood. In the present review, we discuss the possibility that intestinal microbiota influence health through the function of intestinal macrophages.*

### Macrophage Function and Homeostasis

Macrophages play a central role in the innate immune system. They receive primary information by recognizing foreign substances, and transmit this information to other cells by secreting cytokines that promote cell adhesion, migration, and antigen presentation. There are tissue-specific populations of macrophages, such as microglia in the brain and Kupffer cells in the liver. Each tissue-specific macrophage defends the host

against infection and maintains aspects of homeostasis that influence tissue regeneration and metabolic control (1, 2). We hypothesize that homeostasis is regulated by a system comprising a macrophage network because tissue macrophages quickly recognize changes in the external environment and transmit this information globally within the body, a phenomenon termed the macrophage network theory (3).

In the digestive system, the intestinal tract absorbs nutrients and water, and its surface area is approximately 400 m<sup>2</sup> in humans. The intestinal tract is continually exposed to foreign substances, such as intestinal bacteria, and it is therefore not surprising that approximately 60%-70% of the immune cells in the body, including large numbers of macrophages, reside within this organ.

Intestinal macrophages possess phagocytic and bactericidal activities (4), but lack receptors for bacterial components on their cell surface and produce low levels of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-12, and IL-23 (5, 6). These properties possibly explain why the response of intestinal macrophages to foreign substances is highly regulated to prevent adverse effects of inflammation. In contrast, intestinal macrophages may contribute to the maintenance of intestinal homeostasis through the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor- $\beta$  (4). However, the mechanisms responsible for the recognition of foreign substances by intestinal macrophages are unknown.

### Intestinal Macrophages and Disease

Inflammatory bowel diseases (IBDs) are considered autoimmune diseases, and their pathogenesis is not understood. Recently, it has become evident that loss of tolerance of intestinal macrophages to intestinal bacteria is responsible for the pathogenesis of IBDs. The two main clinical manifestations of IBDs are Crohn's disease and ulcerative colitis. In *IL10* knock-out (KO) mice, which are

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used as an animal model of colitis, clinical isolates of *Escherichia coli* and *Enterococcus faecalis* induce IBD (7), whereas germ-free (GF) conditions suppress the development of intestinal inflammation (8). Furthermore, the administration of probiotics prevents intestinal inflammation (9). For example, Kamada *et al.* demonstrated that intestinal macrophages in *IL10* KO mice produce highly elevated levels of IL-12 and IL-23 after challenge with heat-killed *Escherichia coli* or *Enterococcus faecalis* and induce Th1-dependent colitis, whereas IL-10 suppresses production of proinflammatory cytokines in response to recognition of bacteria (10). The immediate precursor of the macrophages is the monocyte. Monocytes are derived from pluripotent stem cells in the bone marrow from where they migrate to different tissues through the circulatory system and differentiate into tissue-specific macrophages (2). Recent studies report that the granulocyte-macrophage colony-stimulating factor (GM-CSF) contributes to differentiation of monocytes to inflammatory-type macrophages (M1 macrophage), whereas the macrophage colony-stimulating factor (M-CSF) contributes to differentiation into anti-inflammatory-type macrophages (M2 macrophage) (11, 12). Kamada *et al.* demonstrated that an M-CSF-rich environment in colonic tissues may contribute to the differentiation of intestinal macrophages into anti-inflammatory M2 macrophages (10). They suggest the possibility that M2 macrophages with an abnormal phenotype contribute to the pathogenesis of intestinal inflammation because monocytes obtained from certain patients with Crohn's disease did not differentiate normally in response to M-CSF stimulation (10). Our previous studies demonstrate that CD14, which normally localizes to the cell surface, was expressed exclusively in the cytoplasm of intestinal macrophages, suggesting that a post-transcriptional mechanism regulates the expression of CD14 at the cell surface (13, 14). We further demonstrated that intestinal macrophages produced TNF- $\alpha$  when stimulated with *Sarcophaga* lectin or by lipopolysaccharide (LPS) after contact with immunoglobulin (Ig) A (15). Therefore, we suggest the possibility that intestinal macrophages mediate an inflammatory response through specific stimulation by IgA.

## Intestinal Microbiota and Diseases

Evidence indicates that intestinal microbiota are involved in the onset of IBD as well as in diseases of the endocrine system (metabolic syndrome), nervous system diseases (depression), and cancer. Diabetes and obesity are characterized by low-grade inflammation accompanying expression of TNF- $\alpha$  by adipose tissue (16). In obese individuals, adipose tissue macrophages convert to the inflammatory phenotype in association with the inflammatory response of adipose tissue (17); however, the molecular basis for this process is unknown. Shi *et al.* found

that nutritional fatty acids activate toll-like receptor (TLR)-4 signaling in adipocytes and macrophages, and that high-fat diets induced inflammatory signaling in adipose cells or tissues, as well as in macrophages (18). TLR4 is a receptor for LPS together with its co-receptor CD14 (19). Cani *et al.* reported that the concentration of bacterial LPS in plasma and the ratio of Gram-negative bacteria to gut microbiota increased during the consumption of a fat-enriched diet and demonstrated that metabolic endotoxemia dysregulates the inflammatory tone and triggers body-weight gain and diabetes (20, 21). Furthermore, CD14-mutant mice did not exhibit certain LPS- and high-fat diet-induced symptoms of metabolic diseases, and that TNF- $\alpha$  production decreased in adipose tissue (20). In a study by Ghoshal *et al.*, LPS was transported to the circulatory system with dietary fat by chylomicrons, suggesting that chylomicron-associated LPS may contribute to post-prandial inflammatory responses or chronic diet-induced inflammation in chylomicron target tissues (22). Thus, it is estimated that changes in intestinal microflora are induced by consumption of an excessively high-fat diet and is associated with increased LPS absorption, resulting in an increase in endotoxemia, which triggers inflammation and metabolic disorders (21).

Elevated risk of colorectal cancer has been associated with high-fat diets, as well as consumption of relatively high amounts of protein, such as red meat and low amounts of vegetables (23, 24). Consumption of high amounts of protein and fat and low amounts of vegetables produces carcinogens in decomposition products (ammonia, hydrogen sulfide, amine, and phenol), secondary bile salts (nitroso-compounds and deoxycholic acid), and reactive oxygen species. This association occurs if the colonic microbiota contains 7 $\alpha$ -dehydroxylating bacteria (chiefly clostridial species), and the primary bile acids are converted to secondary bile acids, such as deoxycholic acid and lithocholic acid (25, 26). It was further shown that risk of cancer increases in the presence of mutagenic reactive oxygen and nitrogen species derived from nitric oxide generated by immune cells such as macrophages (27).

There is increasing evidence suggesting that intestinal microbiota interact with the brain-gut axis and are associated with the maintenance of intestinal homeostasis and neurotransmission (28, 29). For example, in studies of GF mice and specific pathogen-free mice, the microbial colonization process initiates signaling mechanisms that affect neuronal circuits involved in motor control and anxiety (30). The microbiota possibly communicate with the brain-gut axis through different mechanisms as follows: i) direct interaction with mucosal cells (endocrine message), ii) through immune cells (immune message), and iii) through contact with neural endings (neuronal message) (31). Regulatory dysfunction of the gut microflora and brain-gut axis was shown to affect functional gastrointestinal disorders,

such as IBS (30, 32-34). The stress-induced changes of neurotransmitter and pro-inflammatory cytokine levels directly or indirectly affect changes in the composition of the microbiota. For example, norepinephrine (stress hormone) increases the virulence of some bacteria, such as *Escherichia coli* and *Campylobacter jejuni* (35, 36). Pathogenic bacteria in rodents induce anxiety-like behaviors, which are mediated through vagal afferents (34, 37).

### Intestinal Microbiota Maintain Health Through the Function of Intestinal Macrophages

Intestinal microbiota, in contrast to their potential adverse effects, have been shown to contribute to the developmental programming of epithelial barrier function, gut homeostasis, and angiogenesis, as well as the host's innate and adaptive immune responses (38, 39). Probiotics comprise of intestinal microbes, such as *Bifidobacterium* and *Lactobacillus* (40), because these are defined as "live microorganisms that when administered in adequate amounts confer health benefits on the host" (41). Probiotics and intestinal microbiota exert therapeutic effects on conditions such as IBD, stress, anxiety, and cancer.

IL-10 and IL-12, which are produced by macrophages and dendritic cells, play an important role in the mechanisms underlying the therapeutic effects of probiotics. IL-10 and IL-12 production is associated with regulating the balance of Th1/Th2 cells. IL-10 is an anti-inflammatory cytokine that down-regulates phagocytosis and T-cell function, including the production of pro-inflammatory cytokines such as IL-12, TNF- $\alpha$ , and interferon (IFN)- $\gamma$ , which control inflammatory responses (42) and promote the development of regulatory T-cells (43). IL-12 stimulates T-cells to secrete IFN- $\gamma$ , promotes Th1 cell development, and directly or indirectly augments the cytotoxic activity of natural killer (NK) cells and macrophages. IL-12 also suppresses redundant Th2 cell responses that control allergy (44).

IL-10 may improve chronic inflammatory conditions, such as IBD and autoimmune disease (45). In contrast, IL-12 may augment the natural immune defense against infections and cancer (46). The regulation of the macrophage production of IL-10 and IL-12 by probiotics may maintain health and prevent disease. Studies have been conducted to explore these possibilities. For example, Kaji *et al.* reported that IL-10 and IL-12 production by macrophages differs depending on the *Lactobacillus* strain (47). Moreover, IL-12, which causes inflammation when produced in excess, could trigger molecules such as peptidoglycan and induce signaling pathways such as those mediated by TLRs (47, 48). However, most of these studies used peritoneal macrophages and macrophage-derived cell lines, but not intestinal macrophages. As mentioned above, macrophages possess tissue-specific functions. In particular, intestinal

macrophages produce IL-10 but only low levels of IL-12 (10, 49). Therefore, the results of studies on peritoneal macrophages or macrophage cell line cannot be generalized to intestinal macrophages. Elucidation of the function of intestinal macrophages is therefore important to optimize probiotics for preventing and treating enteropathogenic bacterial infections.

### Conclusion

Intestinal microbiota stimulate the intestinal mucosa and influence the health of the host (20-22). To utilize microbiota effectively, it is important to understand how they act, particularly their effects on immune regulation. Numerous studies focusing not only on macrophages but also on NK cells are in progress. We propose here a macrophage network theory that suggests that macrophages are the most important cells for regulating homeostasis. Macrophages are not homogeneous in function and adapt to specific host environments and conditions. Because of this, dysfunction of macrophages may cause serious diseases. The mechanisms that regulate macrophage functions are not yet fully understood. In particular, the functions of intestinal macrophages, which are in most frequent contact with microbiota, are enveloped by a virtual informational 'black box'. For example, why are macrophages that eliminate foreign substances tolerant to intestinal microbiota? How do intestinal macrophages receive and process information from intestinal microbiota? The answers to these questions should facilitate the effective utilization of intestinal microbiota and improve our ability to prevent and treat diseases caused by macrophage dysfunction.

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