Macrophage in intestinal immunity and inflammation: A brief review

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The intestinal epithelium is a single-cell layer that constitutes the largest and most important barrier against the external environment. Intestinal barrier function regulates transport and host defense mechanisms at the mucosal interface with the outside world. Intestinal mucosa provides an effective barrier to microorganisms in health, and is simultaneously semi-permeable, allowing nutrient absorption. Meanwhile, inflammation commonly occurs in the gastrointestinal tract resulting from bacterial infections in the intestine. Macrophages are important in both innate and acquired immunity recognition in the intestinal barrier function, how macrophages can differentiate between pathogens and lactic acid bacteria (LAB) during this process is still complex.

Keywords: Intestinal barrier function; mucosal; macrophages; LAB


Introduction

The intestinal epithelium is a polarized single layer composed of B cells, T cells, granulocytes, mast cells, macrophages and dendritic cells and covered by secretory immunoglobulin A and mucus [1]. Intestinal epithelial cells are responsible for sensing and promoting a host immune response in order to establish a defense upon not only commensal microorganisms but also foreign organisms or particles [2].

Despite the progress made in understanding the immunological aspects of the intestinal barrier function against the external environment, the potential mechanisms of the intestinal barrier are still largely unknown [3]. There has been increasing recognition of an association between disrupted intestinal barrier function and the development of inflammatory diseases over the past decade [4]. Several factors participate in regulation of intestinal barrier function, including the unstirred water layer, mucosal surface hydrophobicity, the surface mucous coat, epithelial and endothelial factors [3]. Inflammatory bowel diseases (IBDs) are complex polygenetic diseases during the intestinal barrier dysfunction, which are believed to involve inappropriate host responses to the complex commensal microbial flora in the gut [6]. The main focus of this brief review will be on the role of macrophage in the normalization of the intestinal barrier and how LAB could influence the immunomodulation through macrophages phagocytosis process.

Immune cells of the intestinal barrier

The intestinal epithelium is a single-cell layer that constitutes the largest and most important barrier against microbial infection [7]. Intestinal homeostasis is coordinated by the responses of different cell types, including both
immune and non-immune cells. The interaction between immune and non-immune cells is amplified by the influx of inflammatory or immune cells, which increases the exposure of non-immune cells to cytokines released from immune cells[8]. This interaction also plays a crucial role in the maintenance of intestinal epithelial homeostasis [9]. Several released mediators, such as histamine, serotonin and mast-cell proteases, as well as newly synthesized mediators, including leukotrienes, prostaglandins, and platelet-activating factor, are able to alter gut function in intestinal barrier by macrophages, leukocytes and mucosal mast cells [10]. Many of these mediators, such as interleukin-4 (IL-4) and tumor necrosis factor alpha (TNF-α) could also affect the epithelial permeability.

In the normal intestinal mucosa, there is a large population of these cells represent the major antigen presenting cell population capable of determining the type of T cell responses that develop to luminal antigens[11]. Macrophage is the major differentiated cell of the mononuclear phagocyte system and important in the host's immunological and inflammatory responses. Of interest is that macrophages seem to have a role in both TH1-driven and TH2-driven responses[3]. Meanwhile, macrophages can express a repertoire of plasma membrane receptors able to recognize all classes of macromolecules. However, these receptors play a broader role in tissue homeostasis within multicellular hosts[12].

**Immune response of intestinal barrier**

Increasing attention has been centered on the gut as a reservoir of bacteria and bacterial toxins in intestinal mucosal barrier function. Meanwhile, inflammation commonly occurs in the gastrointestinal tract resulting from bacterial infections[13-14]. Toll-like receptors (TLRs) play a crucial role in host defense against microbial infection. Meanwhile, the microbial ligands recognized by TLRs are produced by both pathogenic and commensal microorganisms, not unique to pathogens [15]. The key signaling channel is the nuclear factor-kappa B (NF-κB) pathway[16-17]. Although macrophages have long been recognized for displaying innate immune response to bacteria and virus, not much is known about the steady state signaling that sustains such in-built innate immune defense programs. We have recently demonstrated that NF-κB, a transcription factor functioning at the core of our immune system remains activated at a basal level in macrophages in the steady state (Fig.1).

**Phagocytosis processes of macrophages**

Macrophages constitute a fundamental part of innate host defense, phagocytosis is a key mechanism to internalize exogenous materials[18]. In order to discriminate between self and non-self, macrophages have evolved a restricted number of phagocytic pattern recognition receptors, like mannose receptor, that recognize conserved motifs on pathogens and clear the inflammatory molecules[19]. More recent data suggest that the process of phagocytosis itself provides information to phagocytes about the nature of engulfing, which helps to tailor inflammatory responses [20]. An extensive literature shows that murine innate immune cells respond vigorously to various fragments of PGN, and that non-pathogenic LAB demonstrate some regulatory effect on anti-inflammatory responses[21]. Several mechanisms, such as regulation of TLRs expression, negative feedback regulation of the NF-κB pathway and attenuation of NF-κB have been revealed in our previous study. Although there is a growing

![Diagram](Figure 1. NF-κB signaling pathway activation in PGN of *L. acidophilus* mediated anti-inflammation response.)
consumption of such probiotics for their health benefits, the precise mechanisms by which they achieve their effects have remained elusive.

Researchers have also found that the PGN of Staphylococcus aureus can, via phagocytosis, activate nucleotide-binding oligomerization domains (NODs)\(^2^2\). Our research provides a new perspective on the cross-talk between TLR4 and NOD2 in the immune recognition of PGNs from L. acidophilus. Several findings showed that PGN-derived muramyl dipeptide (MDP)-NOD2 and LPS-TLR4 induced IL-1\(\beta\) and TNF-\(\alpha\) production, which provided a better understanding of the delicate regulation of inflammatory response\(^2^3\). And some research also found that long-term NOD2 stimulation contributes to down-regulation of inflammatory responses by innate immune receptors\(^2^4\).

NF-\(\kappa\)B pathway and proinflammatory in macrophages

Inflammatory mediators expressed through NF-\(\kappa\)B pathway that direct the differentiation of monocytes to macrophages, further involving NF-\(\kappa\)B in inflammation-associated metabolic disease\(^2^5\). In NF-\(\kappa\)B-related proinflammation, a network of signaling molecules, transcription factors, epigenetic mechanisms, and posttranscriptional regulators are influenced the forms of macrophage\(^2^6\). During this process, macrophages may undergo classical M\(_1\) activation or alternative M\(_2\) activation\(^2^7\). TLRs engagement leads to inflammation-mediated NF-\(\kappa\)B activation associated with M\(_1\) macrophages, and NF-\(\kappa\)B activation also activates a genetic program essential for resolution of inflammation. Proinflammatory cytokines are cytokines that mediate both acute and chronic inflammation by triggering cascade of inflammatory mediators\(^2^8\). The cell-intrinsic and cell-extrinsic mechanisms work coordinately to regulate the inflammatory response. Among cell-extrinsic mechanisms, the anti-inflammatory cytokine IL-10 limits the inflammatory response through counters activation\(^2^9\). The activated macrophages could release antimicrobial molecules, clear dead cells by phagocytosis to prevent tissue necrosis and eliminate proinflammatory mediators at the cellular level\(^3^1\).

NF-\(\kappa\)B promotes immunity by controlling the expression of genes involved in inflammation and expression of target genes that mediate cell proliferation. NF-\(\kappa\)B activation is tightly controlled by canonical and atypical pathways that regulate proteolysis of I\(\kappa\)B (an inhibitor of NF-\(\kappa\)B) and I\(\kappa\)B-related proteins\(^3^2\). Several probiotic strains can prevent degradation of I\(\kappa\)B, therefore preventing the expression of pro-inflammatory cytokine like IL-8. The cell-intrinsic regulatory mechanisms are various and include those negative regulators which attenuate the NF-\(\kappa\)B inflammatory gene program\(^3^3\). Our present study sought to define the specific pathways involved in PGN’s ability to inhibit the inflammatory process in LPS-induced RAW 264.7 cells. The iTRAQ proteomic analysis indicated that this capacity may first occur in lysosomes during phagocytosis, followed by the calcium signaling pathway, and then lastly the effect is modulated by TLR-4 and its downstream systems, the MKK3/6 dependent NF-\(\kappa\)B pathway. Macrophage relocalization was promoted by activated NF-\(\kappa\)B at the site of infection. Meanwhile, antimicrobial molecules and release chemokines together with leukocytes were recruited to kill pathogens and remove dead cells in the infection site\(^3^4\).

LAB and macrophages phagocytosis in immunomodulation

Gastrointestinal motility and sensory perception are altered in a variety of mucosal inflammatory conditions of the gut, ranging from peptic esophagitis to ulcerative colitis\(^3^5\). The immune system, including its inflammatory components, is fundamental to host defense against pathogenic invaders\(^3^6\). Probiotics such as Lactobacillus acidophilus and Bifidobacterium bifidum have been shown to influence select aspects of immune function. Immune modulation has been observed after administration of LAB in animal studies and a few human studies. Some studies have indicated that the LAB Lactobacillus rhamnosus HN001 can enhance immune function in mice, following oral delivery\(^3^7\). It has been suggested that the anti-tumor effects of LAB were mediated through activated macrophages. Some research also found the phagocytosis of Escherichia coli sp. in vitro was enhanced after the administration of Lactobacillus acidophilus strain La1 or Bifidobacterium bifidum strain Bb 12\(^3^8\). The increment in phagocytosis was coincident with fecal colonization by the LAB, a significant increase inglobal phagocytic activity of blood phagocytes (granulocytes and monocytes) was observed in LAB ingestion groups\(^3^9\). All these founding reveals LAB strains can be used as nutritional supplements to improve the immune function of particular groups.

Summary

Macrophages are important in both innate and acquired immunity recognition in the intestinal barrier function, how macrophages can differentiate between pathogens and lactic acid bacteria (LAB) during this process is still complex. Apart from the inflammatory responses, further study will shed light on the mechanism of macrophage-mediated intestinal epithelial homeostasis and beneficial influence to the host.
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