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Cell signaling in the interaction between pathogenic bacteria and immune cells

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1. ABSTRACT

Cell signaling is an essential part in the complex system of communication that governs basic cellular activities and coordinates cell actions. The ability of cells to perceive and correctly respond to their microenvironment is essential for cell survival and basic biological function. In the defense from pathogenic bacteria, the immune cells exert their function through various signaling pathways. In this review, we will summarize recent findings on the role of cell signaling in the interaction between pathogenic bacteria and immune cells, focusing on neutrophils and macrophages, which are part of the innate immunity, and also T cells, which are components of the adaptive immune system.

2. INTRODUCTION

The immune system consists of the innate and adaptive branches, which together detect pathogens and protect against diseases. Innate cells mediate the activation of the adaptive immune system (1). The innate phagocytes, including neutrophils and macrophages, identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms (2). Both neutrophils and macrophages travel throughout the body in pursuit of invading pathogens (3). On the other hand, the T lymphocytes of adaptive immune system are involved in a cell-mediated immune response, and recognition of the pathogen. Thus, in this study we will focus on neutrophils and macrophages, and also T lymphocytes.

Cell signaling is an essential part in the complex system of communication that governs basic cellular activities and coordinates cell actions. The immune cells may activate certain signaling pathways to participate in disease. In a murine model of polymicrobial sepsis, inhibition of the Toll-like receptor (TLR) 4 could improve the survival (4); the mucosal immune cells respond to TLR-induced nuclear factor kappaB (NF-kappaB) signaling and promote the commensal bacteria-induced colitis (5). Another example is the induction of Ca-signaling in guinea-pig neutrophils and macrophages by lipopolysaccharide (LPS, endotoxin) from gram-negative bacteria (6). Moreover, certain signaling plays a protective role in disease. MyD88 signaling is essential for protection against *Salmonella enterica* serovar Typhimurium infection in innate immune response (7).

On the other hand, the pathogen can mediate the signaling pathways. The *Escherichia coli* alpha-hemolysin-induced mediator is essential for the signal transduction pathway in the interaction between inflammatory cells and granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor (8). During an immune response to a pathogen, signaling transduction pathways play a crucial role in the interaction between immune cells and the pathogen. For instance, a rapamycin-sensitive signaling pathway may act as a negative feedback cascade in the regulatory mechanisms of IL-12 production from monocytes/macrophages induced by *Staphylococcus aureus* (9). In this review, we will summarize the recent studies on signaling pathways in immune cells responding to pathogen.

3. NEUTROPHILS

In the granulocytic anaplasmosis, the obligate intracellular bacterium *Anaplasma phagocytophilum* can lead to a delayed neutrophil apoptosis by the activation

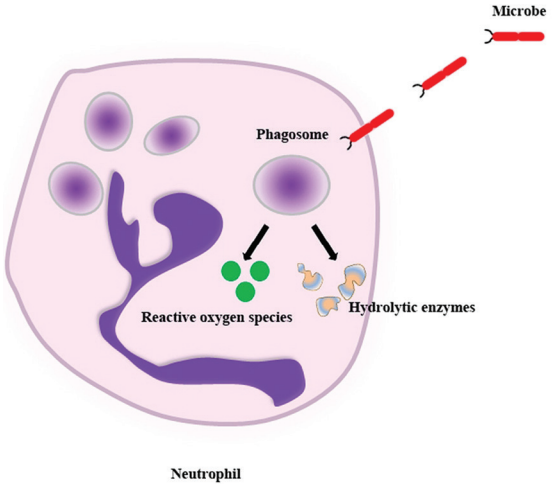

Figure 1. Respiratory burst. During the process of phagocytosis, neutrophils internalize and kill microbes, resulting in the formation of a phagosome, which secrete reactive oxygen species and hydrolytic enzymes.

of the p38/ mitogen-activated protein kinase (MAPK) signaling pathway (10). A study on bacterially intestinal infection found that the NF-kappaB may be a signal for the mucosal influx of neutrophils (11). Thus, pathogens could influence the behaviors of neutrophils via various signaling pathways, leading to disease. Neutrophils are an essential part of innate immune system. When pathogens attack the body, neutrophils play an anti-microbial role by phagocytosis, degranulation and neutrophil extracellular traps. The neutrophil phagocytosis can be strengthened by LFA-1 ligand stimulation, and the LFA-1 counter-receptor, the intercellular adhesion molecule (ICAM)-1 ligand binding, acts as a co-stimulatory signal to induce full phagocytotic function (12). During the process of bacterial phagocytosis, the extracellular response kinase and p38 was stimulated by distinct signal transduction pathways, and the p38 kinase activity is necessary for hydrogenperoxide (H_2O_2) production (13).

The reactive oxygen species, including H_2O_2, are major parts of respiratory burst. During the process of phagocytosis, neutrophils internalize and kill microbes, resulting in the formation of a phagosome, which secretes reactive oxygen species and hydrolytic enzymes, namely respiratory burst (Figure 1). The activation of respiratory burst, measured by tumor necrosis factor (TNF)-triggered H_2O_2 release, can be inhibited by three small compounds screened from 15,000 drug-like compounds generated from 125 combinatorial templates by signaling pathways instead of directly targeting cell components (14). This study also reflects the important role of TNF in the response of neutrophils to pathogen. In truth, TNF turns on phagocyte oxidase through a Ca2+-triggered, soluble adenylyl cyclase-dependent process in the respiratory burst of neutrophils (15).

In the killing of Gram-negative bacteria by neutrophils of patients with cystic fibrosis, the T cell Ig and mucin domain-containing molecule-3 via the ligand galectin-9 is perturbed in the airways due to proteolytic degradation of the receptor (16), suggesting that signaling mediates the interaction between neutrophils and Gram-negative bacteria. Among many types of Gram-negative bacteria, *Pseudomonas aeruginosa* bacteria have attracted much attention. *Pseudomonas aeruginosa* bacteria modulate neutrophil responses of mucoid, especially the interaction with components of the signal transduction pathway, including G proteins and protein kinase C, via their mucoidexopolysaccharide (17). In the rat model of full-thickness wound-healing, polymorphonuclear neutrophils infiltrate into the wound site, in which the Cyclooxygenase-2 is unregulated by the *Pseudomonas aeruginosa* quorum-sensing signal N- (3-oxododecanoyl) homoserinelactone, leading to promoting inflammation (18). Moreover, the Pseudomonas quinolone signal, a quorum sensing molecule produced by bacteria, can stimulate the chemotaxis of polymorphonuclear neutrophils via MAPkinase p38, suggesting that MAPkinase p38 signaling is involved in the influence of bacteria on polymorphonuclear neutrophils (19).

In summary, various signaling pathways participate in the interaction between pathogen and neutrophils. They play crucial roles in the neutrophils' response and killing bacteria, as well as the influence of bacteria on neutrophils.

4. MACROPHAGES

When a pathogen invades in body, the neutrophils move into the site and then proliferate. After the first 48 h, as neutrophils age, they stimulate the appearance of the macrophages, which will then ingest the aged neutrophils as well as the pathogen (20). Each macrophage can digest more than 100 bacteria before it finally perishes together with the pathogen. PI3-kinases (PI3Ks) are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol. PI3Ks participate in a Syk-dependent signaling pathway, which is critical for FcgammaR-mediated phagocytosis and signal transduction in macrophages (21). Nucleotide-binding oligomerization domain 2 signaling promotes macrophages secreting inflammatory cytokines, such as IL-6, TNF-alpha and IL-12p40, in response to bacterial stimulation (22). In the infection of *Mycobacterium avium*, macrophages survival can be improved by phosphorylation of the signal transducer and activator of transcription type 1 (STAT1) signaling pathway (23). These findings suggest that, similar to neutrophils, various signaling pathways are involved in the behaviors of macrophages.

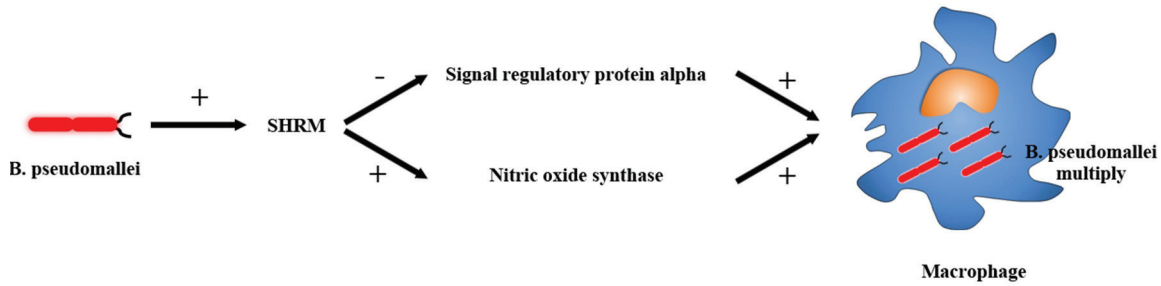

Figure 2. *Burkholderia pseudomallei* multiply in macrophages through SARM signaling. *Burkholderia pseudomallei* induced SARM, which down-regulates signal regulatory protein alpha and up-regulation of nitric oxide synthase, finally facilitating the ability of the bacteria to multiply in macrophages.

On the other hand, the pathogens influence the macrophages via signaling. *Burkholderia pseudomallei* induced SARM, which down-regulates signal regulatory protein alpha and up-regulates nitric oxide synthase, finally facilitating the ability of the bacteria to multiply in macrophages (24) (Figure 2). In tuberculosis, the *Mycobacterium tuberculosis* inhibits class II MHC and change MHC-I Ag processing, leading to a prolonged infection of macrophages, and finally immunologically silencing macrophages and evading surveillance by both CD4+ T and CD8+ T cells, promoting chronic infection (25).

Among other possible examples, we will focus on NF-kappa B and TLR signaling, considering their crucial role in inflammation. The NF-kappaB signaling is significant in the phagocytosis of macrophages that through NF-kappaB activation, *Escherichia coli* prevents the phagocytosis and then leads to enhanced signaling to T cells, thus stimulating the adaptive immune response (26). Through the activation of NF-kappaB signaling, as well as ERK and p38 MAPK signal pathways, the TLR9 was up-regulated by LPS in macrophages, which is an effective response to bacteria invasion (27). Later, Novoselova and colleagues (28) reported similar findings, i.e. that not only NF-kappaB, but also IKK, JNK, TLR2 and TLR4 participate in macrophage's response to toxin from gram-negative bacteria. Although the TLR3 or TLR4 cannot stimulate IFN-beta-mediated innate signal amplification in resident murine alveolar macrophages (29), TLR signaling is crucial in the response of macrophages to pathogens based on findings on NK-kappaB signaling, and different members of the TLR family have diverse roles in different organs and diseases.

The TLRs are also regulated by different signaling cues. The ligomerization of TLR4 is up-regulated by SIGNR1, a member of a new family of mouse C-type lectins, after stimulation with *Escherichia coli*, which is associated with the function of macrophages to capture gram-negative bacteria, and then facilitating signal transduction to activate innate macrophage responses (30). In contrast, TLRs can be negatively regulated by signal regulatory protein alpha, resulting in a decrease of intracellular killing of *Burkholderia pseudomallei* in macrophages (31).

5. T CELLS

T cells play a central role in cell-mediated immunity. In sepsis, STAT signaling network in T cell is reprogrammed within 6 h of bacteremia through secondary signals, whereas macrophages are partially tolerized in their ability to respond to TLR agonists (32). The TLRs are also involved in the interaction between T cells and pathogens. The human bone marrow-derived mesenchymal stem cells express high levels of TLR3 and TLR4, which have the ability to induce NF-kappaB activity and production of IL-6, IL-8 and CXC10, as well as to inhibit T-cell modulatory activity by impairing Notch signaling in Gram-negative bacteria infection (33). The Gram-negative bacteria affect the function of T cells via TLR signaling in T cells. LPS induces human T cells to adhere to fibronectin through TLR4/protein kinase C signaling, as well as phosphorylation of the proline-rich tyrosine kinase (Pyk-2) and p38 (34). In addition to TLR signaling, LPS up-regulates cytokine signaling 3, which is T cell suppressor, leading to inhibition of T cell chemotaxis toward CXCL12 (34).

In different subtypes of T cells, various signaling pathways are involved in the interaction between T cells and pathogens. During bacterial infection, gamma/delta T cells secreting IL-17A/F are negatively regulated by type I IFN (35). As for the secondary infection, activated Wnt signaling is beneficial for memory CD8 T cell formation during the initial immunization, leading to enhanced immunity upon a second encounter with the same pathogen (36). The tetra-acyl LPS acts on both mouse and human dendritic cells, triggering both the CD4+ T and CD8+ T cell responses, whereas only human myeloid dendritic cells favored the induction of regulatory T cells (37).

Pathogens induce functional changes in T cells, but pathogens can be influenced by T cells via signaling pathways as well. Bacteria in the gut secrete

quorum-sensing signal molecules, which are transmitters for bacteria to communicate with one another and participate in the switching of processes including virulence, biofilm formation, sporulation, mating and competence for DNA uptake (38-40). CD4+ T cells play an important role in the initiation of immune responses by helping other cells and taking on a variety of effector functions during immune reactions. Upon antigenic stimulation, naive CD4+ T cells activate, expand, and differentiate into different effector subsets, including T helpers (Th)1, Th2, Th9, Th17, and Th22—that are characterized by the production of distinct cytokines and effector functions (41). Quorum-sensing signal molecules induced apoptosis of CD4+ T cells, particularly CD4+ Th1/Th2, but not CD8+ T cells, in patients with sepsis, which was associated with caspase 3 signaling (42). In the Th1 response to mycobacteria, the CD30L/CD30 signaling promotes the ability of Th1 cell to produce IFN-gamma against bacillus Calmette-Guérin infection (43). The Th1 cell development driven by LPS can be inhibited by TGF-beta signaling, which can also act as an indirect effecter in Th17 cell differentiation (44). The Th17 cells secrete IL-17A and IL-17F, which promote the recruitment and subsequent activation of neutrophils (45-47–208), and IL-17 sustains inflammation, thus amplifying the inflammatory response induced by a preexisting tissue injury (48). The process of Th17 differentiation is controlled by T-cell receptor/ CARD-containing MAGUK protein 1/NF-kappaB signaling via enabling chromatin accessibility of Th17 effecter molecule loci in genetic mouse models (49). In intestinal inflammation, innate expression of Ahr has a protective role in T-cell-mediated experimental colitis by suppressing pathogenic Th17 cells, and Ahr and the commensal flora regulates the balance between innate lymphoid cells and Th17 cells (50).

In summary, different T cell subtypes play various roles in the immune response to pathogens. During these complex processes, different signaling pathways are involved, in which other immune cells or pathogens may influence the T cell function, and in turn, T cells can affect the pathogen via different signaling.

6. CONCLUSIONS

In innate immune cells, such as neutrophils and macrophages, and also in the acquired immune cells T cells, different signaling pathways mediate the interaction between pathogenic bacteria and immune cells. However, in many diseases the roles of different signaling pathways are not very clear, which may be due to technical constraints. As new experimental techniques and methods emerge, more knowledge on roles of various signaling will certainly be acquired. Further understanding on the role of the different signaling pathways in the interaction between pathogenic bacteria and immune cells may provide insights on the function of immune cells and the pathogenesis of bacterial disease, which may be helpful in the development of novel therapeutic strategies.

7. ACKNOWLEDGEMENTS

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Abbreviations: TLR: Toll-like receptor; LPS: lipopolysaccharide; MAPK, mitogen-activated protein kinase; ICAM, intercellular adhesion molecule; TNF: tumor necrosis factor; PI3Ks: PI3-kinases; STAT1, signal transducer and activator of transcription type 1; Pyk-2: proline-rich tyrosine kinase 2; Th: T helpers

Key Words: Pathogenic Bacteria, Immune Cells, Neutrophils, Macrophages, Review

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