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PARASITIC INFECTIONS ACTIVATE TLR4, CD3, IFN-γ, IL-22, AND IL-13: INVOLVEMENT IN INFLAMMATION

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ABSTRACT

Parasites such as protozoa and helminths can infect living things, benefiting at the expense of the host. They are fought by both the innate and adaptive immune responses. The innate response is activated by the binding of the parasite to the Toll-like receptor (TLR)-4 which can recognize specific parts of the parasite. Parasites interact with TLR-4, activating it and inducing an anti-inflammatory immune response, which helps the parasite survive. TLR-4 recognizes pathogen-associated molecular patterns (PAMPs), triggering an innate immune response and the production of pro-inflammatory cytokines such as interferon-gamma (IFN-γ) that help fight the infection. TLRs and the CD3 complex are key components of the immune system in parasitic infections. CD3 is important for signaling from the T-cell receptor (TCR) to the T cell after antigen recognition. In bacterial, viral or parasitic infections, the cytokine IL-22 plays an essential role by helping to maintain the integrity of barrier tissues attacked by microorganisms, particularly in organs such as the intestine, lungs and skin. IL-22 reduces the expression of IL-13-induced M2 markers in macrophages and regulates macrophage Th2 polarization. Activation of the IL-22 receptor (IL-22R) leads to the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT)-3 and 5, which is important for regulating responses to infection-induced cellular stress. IL-13 also plays a key role in immune responses, particularly in parasitic infections by helminth and protozoan parasites. IL-13 is mainly generated by helper T cells and is crucial in mucosal defence against helminths. After a parasitic infection, IL-13 promotes tissue repair and has a fibrotic wound healing effect. The activation of TLR-4, the CD3 complex, and the cytokines IFN-γ, IL-22, IL-13, is fundamental for the immune response against parasites.

KEYWORDS: *Parasite, infection, immune response, Toll-like receptor, inflammation, cytokine*

INTRODUCTION

Parasites include protozoa, helminths, and other organisms that live on or within a host, and benefit at the expense of them (1). The immune system responds to parasitic infections using various pathways related to both innate and adaptive or acquired immunity (2).

The adaptive immune system, mediated by T cells, plays a crucial role in activating specific immune responses to eliminate or kill the parasite and protect against future infections (3). Parasitic infections can have profound effects on T cells, which play a central role in adaptive immunity (4).

However, the immune response varies depending on the type of parasite. For example, helminths can trigger a Th2 immune response, with the release of several cytokines, including IL-13 (5), while intracellular parasites such as

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Plasmodium malaria can activate a Th1 response involving interferon-gamma (IFN-γ) (6). Parasites display highly antigenic molecules on their surface (7) while the outer membrane of Gram-negative bacteria is characterized by the presence of lipopolysaccharide (LPS) that binds Toll-like receptor (TLR) 4, which can recognize specific components of parasites, and activates the innate immune response (8). However, parasites have developed sophisticated mechanisms to evade or manipulate host immune responses, including interactions with TLRs (9).

DISCUSSION

TLR-4 is often associated with bacterial infections, and in parasitic infections, it can help recognize certain components of the parasite and activate an immune response (10). TLR-4 is a pattern recognition receptor (PRR) found on infectious agents such as bacteria, viruses, fungi, and parasites. When TLR-4 recognizes pathogen-associated molecular patterns (PAMPs), it triggers an immune response that helps fight the infection (11). TLR-4 is a pattern recognition receptor (PRR) found on immune cells such as macrophages and dendritic cells (12). Activation of TLR-4 leads to the production of pro-inflammatory cytokines such as IFN-γ, which enhances parasite clearance (13). Helminths can modulate the host immune system by interacting with TLR-4 (14).

Parasites can release molecules that activate TLR-4, which can lead to a regulatory or anti-inflammatory immune response, which helps the parasite survive within the host (15). For example, the blood fluke *Schistosoma mansoni* releases lipids that can bind to TLR-4, triggering immune responses that dampen inflammation and allow the parasite to persist (16). Additionally, Leishmania species, which cause leishmaniasis, are recognized by the immune system through various TLRs, including TLR-4 (17). Parasite surface molecules, such as lipophosphoglycan (LPG), can interact with TLR-4 to modulate the host immune response (18). Evidence suggests that Leishmania can suppress TLR-4-mediated responses, evading the immune system (19).

Parasites often manipulate TLR signaling to promote chronic infection by inducing anti-inflammatory responses, altering the cytokine milieu, or blocking full activation of the immune system (20). For example, helminths often shift the host immune response from a pro-inflammatory Th1 or Th17 response to a more anti-inflammatory Th2 response, thereby avoiding strong immune attacks (21). Similarly, some parasites reduce TLR-4 signaling to avoid triggering a potent immune response (22).

TLRs and the CD3 complex are critical components of the immune system, and both play distinct but complementary roles in the response to parasitic infections (23). The CD3 complex consists of several proteins such as CD3γ, CD3δ, CD3ε, and CD3ζ, and is essential for transmitting the signal from the TCR to the T cell after it recognizes an antigen presented by the major histocompatibility complex (MHC) on antigen-presenting cells (APCs) (24).

CD3 is a protein complex present on the surface of T cells and is essential for activating the specific response of T cells by antigen, which forms the basis of adaptive immunity (25). CD3 is part of the T-cell receptor (TCR) complex, which is essential for activating T cells. All T cells express CD3 cells, which help transmit signals into the T cell once the TCR binds to an antigen. In parasitic infections, the number and function of CD3+ T cells is critical to mounting an effective immune response (26). In particular, CD4+ helper T cells guide other immune cells, while CD8+ cytotoxic T cells kill infected cells.

The CD3 receptor binds the anti-CD3 monoclonal antibody to the membrane of T cells. This practice is used in immunotherapy to suppress the immune response in some immune disorders such as autoimmune diseases or to prevent transplant rejection. Anti-CD3 T cells dump the immune response, increasing the risk of infection (27). Anti-CD3 therapy inhibits T lymphocytes, which are essential for fighting infections. Therefore, immunosuppression with anti-CD3 increases susceptibility to infections by parasites and viruses such as cytomegalovirus, herpes simplex, and Epstein-Barr virus. In addition, anti-CD3 treatment can cause cytokine release syndrome, a serious side effect in which a strong immune response leads to fever, inflammation, and increased risk of infection (28).

Bacterial, viral, fungal, or parasitic infections trigger immune responses in which the CD3 receptor and cytokines such as IL-22 play essential roles (29). IL-22 helps maintain the integrity of barrier tissues attacked by microorganisms, while CD3 supports the adaptive immune response to directly fight the infection (30). IL-22 is a signaling cytokine involved in immune responses, particularly in mucosal immunity (e.g., skin, gut, respiratory tract). IL-22 helps protect tissues from damage during infection by promoting tissue repair and the production of antimicrobial peptides (30). It is essential for the defense against bacterial and parasitic infections, particularly in organs such as the gut, lungs, and skin (31).

IL-22 does not act directly on immune cells, but targets epithelial cells, promoting barrier function and defense against pathogens by inducing the secretion of immune molecules. Furthermore, IL-22 reduces the expression of M2 markers such as CD163 and CD200R induced by IL-13 in macrophages (32). IL-22+ cells regulate Th2 polarization of macrophages during Schistosoma infection and negatively influence liver fibrosis by acting directly on hepatic stellate cells, which are pericytes found in the perisinusoidal space, a small area between the sinusoids and the hepatocytes of the liver (called the space of Disse) (33). Engagement of the IL-22 receptor (IL-22R) leads to the activation of several downstream signaling pathways, most notably the phosphorylation of p38 MAPK, STAT3, and STAT5 (34).

IL-22 binds to its receptor IL-22R1 and IL-10R2 to activate the p38 MAPK kinase, a biochemical cascade that regulates cellular stress responses, inflammation, and cytokine production (35). IL-22 signals primarily through the JAK/STAT pathway, where binding of IL-22 to IL-22R activates the receptor-associated Janus kinases JAK1 and Tyk2 (36). These kinases phosphorylate STAT3, which subsequently dimerizes and translocates to the nucleus (37). This reaction induces the transcription of target genes involved in inflammation, survival, and tissue repair (38). Binding of IL-22 to its receptor IL-22R can also lead (with less intensity than the previous reaction) to the phosphorylation of STAT5. Phosphorylated STAT5 may have overlapping or distinct roles in immune regulation. Activated IL-22R triggers the phosphorylation of p38 MAPK, STAT3, and STAT5, influencing processes such as inflammation, cell survival, tissue homeostasis, and immune responses. These pathways are critical in several diseases, including parasitic infections.

IL-22 and IL-13 are cytokines that play key roles in immune responses, especially in parasitic infections involving helminths and protozoan parasites (39). Their roles in immune defense against parasites and inflammation are distinct but complementary.

IL-13 is a Th2-type cytokine, meaning it is typically produced by T helper 2 (Th2) cells, a subset of CD4+ T cells (40). It is involved in regulating effective immune responses against extracellular parasites, particularly helminths. IL-13 plays a key role in the body's response to infection and is produced primarily by type 2 T helper (Th2) cells, which are involved in orchestrating immune responses against extracellular pathogens, including parasites. IL-13 is an important cytokine in mucosal defense and protection against external insults, including infections that infect tissues such as the gut, skin, and lungs (41). This cytokine promotes mucus production by goblet cells in the intestinal lining, helping to expel the infectious agent. During helminth infection, IL-13 not only promotes tissue repair but can also mediate a fibrotic wound healing effect by stimulating collagen production in fibroblasts (42). In addition, IL-13 induces smooth muscle hypercontractility in the intestine, promoting expulsion of worms with the help of increased peristalsis (43).

CONCLUSIONS

Parasitic infections activate several immune and inflammatory processes involving the TLR-4 and CD3 receptors, which, once activated, lead to a biochemical pathway with release of cytokines such as IFN-γ, IL-22, and IL-13. However, despite the remarkable progress in understanding the processes described above, the precise nature of the immune response to infections and its regulatory mechanisms remain unclear.

Conflict of interest

The authors declare that they have no conflict of interest.

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