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MOLECULAR MECHANISMS OF CYTOKINE RECEPTOR SIGNALING IN INFECTION

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ABSTRACT

Cytokine receptor signaling is fundamental to the immune system's ability to respond to infections. The intricate signaling networks activated by cytokine-receptor interactions ensure a coordinated and effective immune response. The main families of cytokine receptors include: type I and type II cytokine receptors, which bind to ILs, interferons (IFNs), and colony-stimulating factors (CSFs) and signal through the Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway; tumor necrosis factor (TNF) receptors, which bind TNF cytokines and primarily signal through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways; interleukin (IL)-1 receptors, which bind IL-1 and signal through the MyD88-dependent pathway, leading to NF-κB activation; and G protein-coupled receptors (GPCRs), which bind chemokines and signal through G proteins, leading to changes in cellular calcium levels and activation of various kinases. Dysregulation of these pathways can lead to inadequate immune responses or chronic inflammatory diseases, highlighting the importance of understanding these mechanisms for developing targeted therapies.

KEYWORDS: *cytokine, receptor, signaling, infection, immunity*

INTRODUCTION

Cytokines are small proteins that are crucial for cell signaling in the immune system. They regulate various immune responses, including inflammation, infection control, and tissue repair. Cytokine receptors are present on the surface of immune cells and mediate the effects of cytokines. Understanding cytokine receptor signaling is essential for comprehending how the immune system responds to infections and maintains homeostasis.

Cytokines are secreted *in vitro* by immune cells, usually in response to a stimulus, and induce activities such as growth, differentiation, and cell death (1). Their action is usually local but can sometimes occur throughout the entire organism. Cytokines can have an autocrine effect, acting on the same cell that they were secreted from, or a paracrine effect by acting on adjacent cells. Some cytokines can also act in an endocrine manner, affecting cells very distant from them (2). They have a half-life of a few minutes and are non-antigen specific (3). These small protein molecules regulate different types of immune responses and tissue repair, but also the inflammatory process, aggravating the pathological state (1).

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Cytokine receptors are located on the surface of immune cells and can be activated by various protein substances, including cytokines themselves and microorganisms. These reactions are important for understanding how the immune system reacts to infectious agents.

Cytokine receptors are classified based on their structural features and the signaling pathways they activate. The major families include type I and type II cytokine receptors, tumor necrosis factor (TNF) receptors, interleukin (IL)-1 receptors, and G protein-coupled receptors (GPCRs).

DISCUSSION

Type I and type II cytokine receptors bind to cytokines such as ILs, interferons (IFNs), and colony-stimulating factors (CSFs) (4). They typically signal through the Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway. TNF Receptors bind TNF cytokines and primarily signal through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (5). IL-1 receptors bind IL-1 and signal through the MyD88-dependent pathway, leading to NF-κB activation (6) (Fig.1). GPCRs bind chemokines and signal through G proteins, leading to changes in cellular calcium levels and activation of various kinases (7).

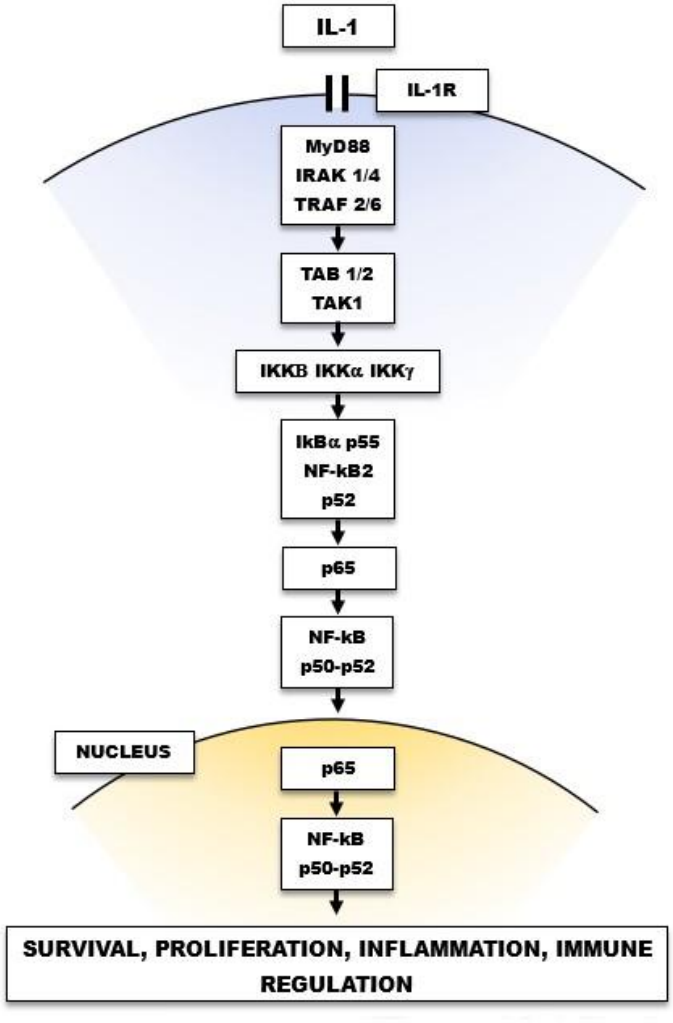

Fig. 1. *IL-1 is a cytokine which exerts multiple effects on cells by binding the IL-R. This activation leads to the generation of NF-kB and p50-p52, which causes the release of proteins in the nucleus that mediate inflammation, immune regulation, survival, and proliferation.*

The JAK-STAT pathway is one of the signaling cytokine receptors. Its activation allows the binding of the cytokines IL-6, IL-10, and IFNs to their receptors and leads to the activation of associated JAKs (8). Activated JAKs lead to phosphorylation of tyrosine residues on the receptor, creating docking sites for STAT proteins (8,9). Phosphorylated STATs dimerize and translocate to the nucleus, where they regulate gene expression (10).

Lipopolysaccharide (LPS) is a gram-negative bacteria which activates immune cells that have CD14 receptors (11). The NF-kB activation pathway is implicated in the binding of cytokines, such as TNF to TNF receptors and IL-1 receptors to IL-1, which activates IkB kinase (IKK) (12). Subsequently, the degradation of IkB occurs with the phosphorylation of IKK in IkB with the release of NF-kB (13). Once activated, free NF-kB translocates into the nucleus and activates genes involved in inflammation and the immune response (12) (Fig.2).

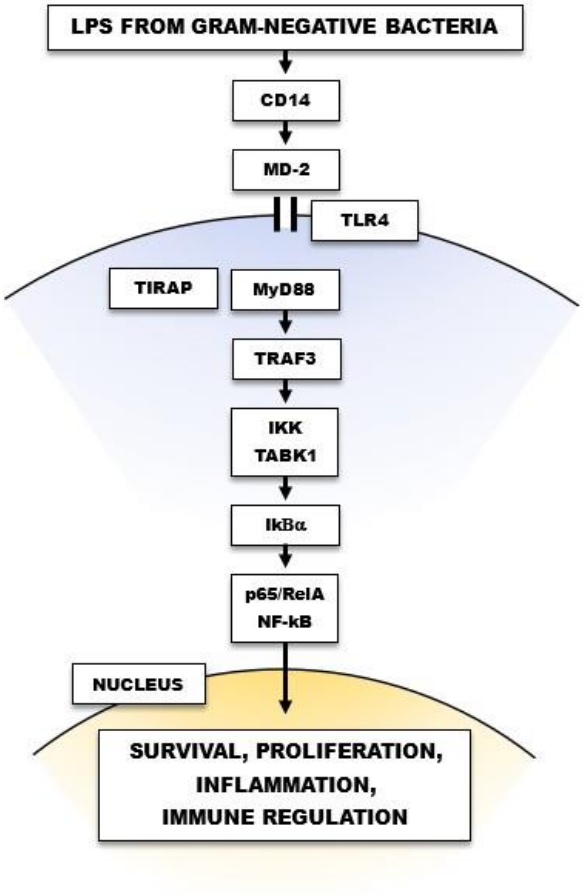

Fig. 2. *Lipopolysaccharide (LPS) activates the CD14 receptor and MD-2 to stimulate the toll-like receptor 4 (TLR4) on the cell membrane. This leads to a biochemical pathway cascade that activates NF-kB, which enters the nucleus and affects genes that code for proteins which mediate inflammation, immune regulation, survival, and proliferation.*

In the activation of the MAPK pathway, the binding of cytokines activates the kinases associated with the receptors that phosphorylate the MAPKs (14). The MAPK cascade involves three main kinases: MAPK kinase kinase (MAP3K), MAPK kinase (MAP2K), and MAPK. Activated MAPKs enter the nucleus and regulate the expression of genes involved in cell growth, differentiation, and the immune response (14).

In activation of the GPCR pathway, binding of chemokines to GPCRs activates heterotrimeric G proteins by exchanging GDP for GTP (15). Regarding signal transduction, G proteins dissociate into Gα and Gβγ subunits that activate downstream effectors such as adenylate cyclase, phospholipase C, and various kinases (16). All these pathways exert regulation of cellular responses, including activation, adhesion, and chemotaxis (17).

Cytokine receptor signaling is critical for orchestrating the immune response to infection (18). By binding to their receptors, cytokines exert important signals to enhance the immune response against infectious microorganisms (19). On the other hand, certain cytokines stimulate PIP3, activating Akt, which inhibits the cell cycle (20) (Fig.3).

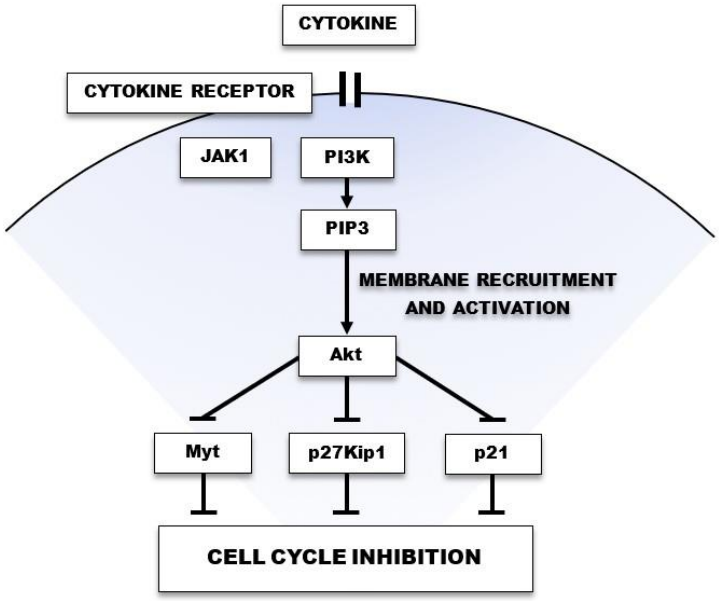

Fig. 3. *Activation of cytokine receptors may lead to Akt membrane recruitment and activation which inhibits Myt, p27Kip1, and p21, leading to inhibition of the cell cycle.*

Infection stimulates the innate immune response with the production of pro-inflammatory cytokines such as IL-1, TNF, IL-6 and IFN, which activate the NF-kB and MAPK metabolic pathways to initiate inflammation, recruit immune cells, and enhance the elimination of pathogens (1,21). In the adaptive immune response, cytokines such as IL-12, promote the differentiation of T cells into Th1 cells, which are crucial for fighting intracellular pathogens (22). IL-4 promotes the differentiation of Th2 cells, which are important for combating extracellular pathogens (23). IFNα and β activate the JAK-STAT pathway, inducing the expression of antiviral genes that inhibit viral replication and improve antigen presentation (24).

CONCLUSIONS

Cytokine receptor signaling is important for the development of the immune system against infectious pathogen antigens. The different signals of activation of cytokines linked to their receptors can lead to an effective immune response against infectious microorganisms but can also lead to hyperinflammation due to the release of pro-inflammatory cytokines. The study of these mechanisms can lead to improvements in the treatment of inflammatory and autoimmune diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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