EDITORIAL

Antimycobacterial Immune Response Regulators: Cytokine Receptors

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ABSTRACT

Cytokine receptors are important regulators of the antimycobacterial immune response, as they help to initiate and coordinate immune cell recruitment and activation during infection. They identify and bind certain cytokines, and they play a role in generating intracellular signal transduction pathways that control a variety of biological activities such as cell proliferation, differentiation, metabolism, and growth. Defective signalling may contribute to greater vulnerability to mycobacteria due to abnormalities in cytokine receptor genes, allowing organisms to elude death and immune surveillance. The consequences of receptor gene abnormalities for the course of mycobacterial infection are discussed in this work, which provides an overview of cytokine receptors critical for innate and adaptive immune responses against mycobacteria contextualized needs for the cardiac patients in Namibia.

Key Words: *Cytokine; cytokine receptors; immune response*

INTRODUCTION

Mycobacterium tuberculosis (MTB), the causative agent of Tuberculosis (TB), has a variety of distinguishing characteristics. Tubercle bacilli dormancy is caused by the pathogen's extraordinary ability to live and proliferate extracellularly both in vivo and in vitro; its cell envelope is mostly composed of a complex of lipids and carbohydrates; and the pathogen's extraordinary ability to persist within host macrophages . The pathogen's interaction with innate and adaptive immune cells is complex, including cytokine/chemokine-mediated host defences. Mtb infiltrates the pulmonary alveolus by delivering bacteria-containing droplets. The efficacy of Mtb colonisation depends to some extent on the size of droplets.

For several reasons, 0.5–5 micrometre droplets are considered to be more effective carriers of mycobacteria than those of 5–10 micrometres: they persist in the air for 2 to 40 hours, they are transmitted over a greater distance, and they are inhaled more efficiently into the tracheobronchial tree and alveolar space. Airway Epithelial Cells (AEC), alveolar type II pneumocytes, alveolar macrophages, dendritic cells (DC), and neutrophils are all affected by Mtb. Mycobacteria infects the airway epithelial cells, alveolar type II pneumocytes, and alveolar macrophages initially [5]. They respond by generating early inflammatory mediators such as tumour necrosis factor (TNF)-, interleukin (IL)-1, interferon (IFN)-, and chemoattractants such as IL-8 (CXCL8), which attracts neutrophils, monocytes, and macrophages from blood vessels.

When DC arrive at the infection site, they acquire mycobacterial antigens by ingesting Mtb or its breakdown products, as well as swallowing the apoptotic bodies created by dying neutrophils and macrophages, which contain both living and dead Mtb. When DC come into contact with Mtb antigens, they produce more IL-12 and IFN-. IFN- controls the release of IP-10 (CXCL10), a chemokine that attracts NK cells, during the early stages of infection. Antigen-Presenting Cells (APCs), such as DC and macrophages, identify Mtb ligands, such as lipoproteins and glycolipids, via pattern recognition Receptors (PRR), such as Toll-Like receptors (TLR) and Nucleotide-binding oligomerization domain (NOD) proteins, resulting in the production of inflammatory cytokines and chemokines.

Infected APCs travel to draining lymph nodes in the area, where they begin to establish acquired immunity by presenting antigen to naive T cells. Mtb-specific T cells have been seen in the lungs of mice 1–3 weeks after infection, and this has been linked to the generation of IFN- by CD4+ T cells and the management of bacterial load. In addition, IFN-producing CD4+ T cells support other T cell subsets, such as CD8+ T cells and T cells, which are critical in reducing Mtb infection. Mtb antigens are given to CD4+ T lymphocytes via MHC class II molecules, causing them to become activated. MHC class I molecules also present Mtb peptides to CD8+ T lymphocytes.

T cells without APCs detect Mtb phosphoantigens, which induce the synthesis of perforin and granzymes, which kill infected immune cells with Mtb inside them. In addition, in response to intracellular infections, they can generate IFN- and TNF- . Although effector and memory T cells are important for suppressing Mtb infection, researchers are concentrating their efforts on the CD4-based immune response, particularly CD4 cells that generate IFN-, because the CD8 response appears to play a much smaller role.

DC travel from the lungs to local draining lymph nodes after Mtb absorption, where they offer Mtb antigens to T cells. T cells return to the infection site in the lungs and have a role in granuloma development.

The primary function in granuloma formation is attributed to many effector cytokines, among which TNF-α and IFN-γ are particularly essential in TB. Macrophages are found at the granuloma's centre, whereas lymphocytes make up the periphery layer. TNF serves a dual purpose: on the one hand, it inhibits bacterial growth; on the other hand, too much of it in the microenvironment, combined with strong T-cell immunity, can cause macrophage necrosis and destabilise the granuloma structure, allowing mycobacteria to escape and proliferate uncontrollably. Newly infected macrophages have low antimicrobial activity and only have a minor effect on Mtb development via TNF-dependent pathways.

Cell-to-cell communication is facilitated by cytokines and chemokines, which also play important roles in cell migration and immune response development the course of immunological events during Mtb infection, cytoskine/chemokine synthesis and their potential to modulate immune cell responsiveness through cytokine binding to specific receptors is critical. In this paper, we look at the receptors for cytokines and chemokines that play a key role in the antimycobacterial immune response, as well as their role in disease development and dormancy. Understanding the role of cytokine/chemokine receptors in the response to Mtb infection is critical for TB control.

Involvement of Cytokine Receptors in Antimycobacterial Immune Response

Type I cytokine receptors are cell surface transmembrane receptors that recognise four-helix bundle cytokines including IL-2, IL-4, IL-6, IL-12, IL-23, Granulocyte Colony-Stimulating Factor (G-CSF), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) (GM-CSF). The lack of intrinsic protein tyrosine kinase activity and signal transduction through the participation of non-receptor Janus Kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs) factors are the common features of these receptors. They're made up of many amino acid chains that have similar intracellular and extracellular characteristics.

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The haemopoietin domain, also known as the Cytokine Receptor Homology Hegion (CHR), is formed by a pair of Fibronectin type III (FnIII) modules, and it is at the junction of these modules that the principal cytokine binding site is found. The first III domain of CHRs has four conserved cysteine residues, and the second FnIII domain has a tryptophan-serine-X-tryptophan-serine (WSXWS) pattern. The WSXWS sequence acts as a recognition site for protein-protein interactions, and cysteines are essential for the structural and functional integrity of receptors. Extracellular domains like as immunoglobulin (Ig) domains, extra FnIII domains, or even a second CHR are found in many type I cytokine receptors.

IL-2, a primary T-lymphocyte growth factor, increases T-cell proliferation and maturation while also controlling B cell proliferation and natural killer (NK) cell cytolytic activity. The receptor structure for IL-2, the first short-chain type I cytokine, has been found. The functional IL-2 receptor (IL-2R) comes in three different forms, each of which is made up of three separate chains: IL-2R (CD25), IL-2R (CD122), and IL-2R (CD132). Signal transduction is carried out by the IL-2R and c components of the type I cytokine receptor family. The chains are expressed in diverse ways on different cell types, and they can assemble in a variety of ways to bind IL-2 with low, moderate, or high affinity.

The chains are expressed in diverse ways on different cell types, and they can assemble in a variety of ways to bind IL-2 with low, moderate, or high affinity. The IL-2R subunit has a poor affinity for IL-2, but when it is combined with c, it creates an intermediate-affinity IL-2R, and the three-chain complex has a high affinity for the cytokine. The IL-2R subunit binds IL-2 first, causing it to alter conformation and boost its affinity for the IL-2R and c subunits. The Janus family of tyrosine kinases JAK1 and JAK3, which are linked with IL-2R and c, respectively, are activated by IL-2 stimulation and phosphorylate IL-2R, causing tyrosine phosphorylation of STATs and other downstream substrates. Three primary signal transduction systems are involved in the downstream signalling pathways induced by IL-2.

IL-4 Receptor

IL-4 is a pleiotropic type I cytokine that plays an important role in immune response control. IL-4 causes the development of naive CD4 T cells into type 2 helper Th2 cells, the switch of Ig class in B cells to IgG1 and IgE, and alternative macrophage activation. The type I IL-4R and the type II IL-4R are two surface receptor complexes that the cytokine interacts with to carry out its biological functions. The IL-4R CD124) chain, which is a functioning receptor subunit, is found in both receptor types.

The interaction of the IL-4R subunit with the C subunit (CD132) produces type I IL-4R, while the interaction of the IL-4R subunit with the IL-13 binding chain, IL-13R1 CD213a1 produces type II IL-4R. The IL-4R chain is also a subunit of the IL-13 receptor (IL-13R), which explains why IL-4 and IL-13 have similar biological effects. When IL-4 binds to the IL-4R extracellular domain, the intracellular receptor domains undergo a conformational shift, which activates the receptor-associated Janus kinases, causing STAT6 to be recruited and phosphorylated. STAT6 that has been activated generates homodimers that translocate to the nucleus and increase transcription of IL-4-responsive genes.

IL-6 Receptor

A IL-6 is a multifunctional cytokine with significant immunomodulatory activity that was first found as a B-cell differentiation factor. It regulates the acute phase response, inflammation, immunological response, and haemopoiesis, among other things. Through its specific receptor system, the cytokine has an impact on a variety of cell types. The IL-6-binding receptor complex is made up of two parts: the IL-6 receptor subunit (IL-6R), which can be membrane-bound mIL-6R or soluble sIL-6R, and the IL-6 signal transducing chain glycoprotein 130 gp130. Although cells that lack IL-6R do not respond to IL-6 alone, the complex produced by IL-6 and sIL-6R can stimulate them. When IL-6 binds to mIL-6R, homodimerization of gp130 occurs, forming a high-affinity IL-6/IL-6R/gp130 complex that activates a variety of biological signals via two pathways: JAK/STAT and NF-kB.

IL-12 Receptor

IL-12 is a major immunoregulatory cytokine that is made up of two covalently linked subunits, IL-12p35 (35 kDa) and IL-12p40 (40 kDa), that are expressed on separate chromosomes. The cytokine is involved in the synthesis of interferon (IFN)-gamma () and the differentiation of CD4+ T cells into the type 1 T helper (Th1) phenotype, which is critical for cell-mediated immune responses against a variety of intracellular pathogens. IL-12's biological effects are mediated by binding to the membrane IL-12 receptor (IL-12R) complex, which is made up of two chains: IL-12R1 (CD212) and IL-12R2 (CD212). Following the binding of IL-12p40 and IL-12p35 subunits to IL-12R1 and IL-12R2, JAK kinases are activated (Tyk-2 and Jak-2). The JAK/STAT pathway phosphorylates IL-12R2, which serves as a docking site for STAT4 proteins.

The expression of IL-12R was revealed to be critical for the maturation of Th1 IFN-producing cells. According to Zhang et al., the percentage of T cells expressing IL-12R1 and IL-12R2, as well as the levels of IL-12R2 mRNA in Mtb-stimulated peripheral blood mononuclear cells, were considerably lower in TB patients compared to controls. IL-12R2 mRNA expression was enhanced in the pleural fluid and lymph nodes of patients with active tuberculosis. Anti-IL-10 and anti-TGF- antibodies increased IL-12R1/IL-12R2 expression and IFN- production by Mtb-stimulated peripheral blood T cells from TB patients, implying that increased TGF- production could lower IL-12R1 and IL-12R2 expression in active TB. It also shows that the expression of IL-12R1 and IL-12R2 plays an important function.

CONCLUSION

During mycobacterial infection, cytokine receptors are crucial for coordinating immunological and inflammatory responses. The major data comes from investigations in animal models as well as observations in people with cytokine receptor or signalling pathway genetic abnormalities. Understanding their exceptional characteristics can lead to novel techniques for immunological intervention in tuberculosis and other mycobacterial diseases, as well as new insights into the processes of antimycobacterial immunity.

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