Chapter

Cytokine Profiling Plays a Crucial Role in Activating Immune System to Clear Infectious Pathogens

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Abstract

Pathogen infections are recognized by the immune system, which consists of two types of responses: an innate immune response that recognizes pathogen-associated molecular patterns (PAMPs) and an antigen-specific adaptive immune response. In both responses, there are several activated cells of the immune system, which play a key role in establishing the environment of cytokines, thus directing their differentiation either suppressing or promoting the immune response. This immune response is crucial against pathogen infections. In this chapter, we will describe the crucial role played by different families of cytokines during activation of the immune system to eliminate infectious pathogens.

Keywords: cytokines, IL-1, TNF, IL-17, IL-6, IFN, bacteria, fungi, virus, parasites

1. Introduction

The innate and adaptive immune responses are key factors in the control of infections or chronic diseases. The balance between these two systems is mainly orchestrated by cytokines [1]. Cytokines are low-molecular-weight proteins that contribute to the chemical language that regulates the development and repair of tissues, hematopoiesis, inflammation, etc., through the transduction of signals mediated by binding to cellular receptors. Cytokines can act on their target cells in an autocrine, paracrine, and/or endocrine fashion to induce systemic and/or localized immune responses. In addition, cytokines have pleiotropic activity, that is, they act on different target cells, as well as affect the function of other cytokines in an additive, synergistic, or antagonistic manner [2, 3]. Cytokines can be secreted by immune cells, but they can also be produced by a wide variety of cells in response to infection or can be produced or released from cells in response to cellular damage when cellular integrity is compromised. Acting through a series of conserved signaling pathways that program transcriptional pathways by controlling many biological processes, such as cell growth, cell differentiation, apoptosis, development,

and survival, can also reprogram cells in the local tissue environment to improve certain types of immune responses. Therefore, cytokines are critical mediators of communication for the immune system and are essential for host defense against pathogens [4].

2. Cytokines

The cytokine pattern that is released from the cell depends primarily on the nature of the antigenic stimulus and the type of cell being stimulated. Cytokines compromise leukocytes to respond to a microbial stimulus. Cytokines can be classified into six groups: (1) L1 superfamily, (2) TNF superfamily, (3) IL-17 family, (4) IL-6 superfamily, (5) type I superfamily, and (6) type II superfamily [5].

2.1 IL-1 superfamily

More than any other cytokine family, the interleukin (IL)-1 family of ligands and receptors is primarily associated with acute and chronic inflammation. The cytosolic segment of each IL-1 receptor family member contains the Toll/interleukin-1 receptor (TIR) domain. This domain is also present in each Toll-like receptor (TLR), which responds to microbial products and viruses [6]. Since TIR domains are functional for both receptor families, responses to the IL-1 family are fundamental to the innate immunity [7].

2.1.1 IL-1 family of cytokines and innate immune system

There are 11 members of IL-1 family of cytokines (IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-36Ra IL-37, and IL-38) and 10 members of the IL-1 family of receptors (IL-1R1 to ILR10) [8, 9]. More than any other cytokine family, the IL-1 family members are closely linked to damaging inflammation; however, the same members also work to increase nonspecific resistance to infection and the development of an immune response to a foreign antigen [10].

The numerous biological properties of the IL-1 family are nonspecific. The importance of IL-1 family members to the innate response became evident upon the discovery that the cytoplasmic domain of the IL-1 receptor type 1 (IL-1R1) is also found in the Toll protein of the fruit fly. The functional domain of the cytoplasmic component of IL-1R1 is termed the TIR domain. Thus, fundamental inflammatory responses such as the induction of cyclooxygenase type 2 (COX-2), production of multiple cytokines and chemokines, increased the expression of adhesion molecules, or synthesis of nitric oxide (NO) are indistinguishable responses of both IL-1 and TLR ligands [11]. Both TLR and IL-1 families nonspecifically augment antigen recognition and activate lymphocyte function. The lymphocyte-activating function of IL-1 was first described in 1979 and is now considered a fundamental property of the acquired immune response. IL-1β is the most studied member of the IL-1 family due to its role in mediating auto-inflammatory diseases. Unquestionably, IL-1β evolved to assist host defense against infection, and this landmark study established how a low dose of recombinant IL-1β protects mice against lethal bacterial infection in the absence of neutrophils. Although we now accept the concept that cytokines like IL-1β served millions of years of evolution to protect the host, in the antibiotic and antiviral therapies era of today, we view cytokines as the cause of disease due to acute or chronic inflammation [12]. IL-1β has emerged as a therapeutic target for an expanding number of systemic and local inflammatory conditions called auto-inflammatory diseases. The neutralization of IL-1β results in a rapid and

sustained reduction in disease severity. Treatment for autoimmune diseases often includes immunosuppressive drugs, whereas neutralization of IL-1β is mostly anti-inflammatory. The auto-inflammatory diseases are caused due to gain-of-function mutations for caspase-1 activity, and common ailments, such as gout, type 2 diabetes, heart failure, recurrent pericarditis, rheumatoid arthritis, and smoldering myeloma, respond to the IL-1β neutralization [7]. IL-1 family also includes member that suppress inflammation, specifically within the IL-1 family, such as the IL-1 receptor antagonist (IL-1Ra), IL-36 receptor antagonist (IL-36Ra), and IL-37. In addition, the IL-1 family member IL-38, the last member of the IL-1 family of cytokines to be studied, nonspecifically suppresses inflammation and limits the innate immunity [12].

2.1.2 IL-1 receptor family

There are 10 members of the IL-1 family receptors. IL-1R1 binds IL-1α, IL-1β, and IL-1Ra and IL-R1 binds either IL-1β or IL-1α. IL-1R2 is a decoy receptor for IL-1β. IL-1R2 lacks a cytoplasmic domain and exists not only as an integral membrane protein but also in a soluble form. The term soluble is meant to denote the extracellular domain only. The soluble domain of IL-1R2 binds IL-1β in the extracellular space and neutralizes IL-1β. The neutralization of IL-1β by soluble IL-1R2 is greatly enhanced by forming a complex with IL-1R3. IL-1R3 is the co-receptor for IL-1α, IL-1β, IL-33, IL-36a, IL-36β, and IL-36γ. IL-1R3 exists as an integral membrane receptor or in a soluble receptor form. The inflammation and infection drive liver to increase the synthesis and levels of soluble IL-1R3 in the circulation [13].

2.2 TNF superfamily

Tumor necrosis factor superfamily (TNFSF) is a group of cytokines composed of 19 ligands and 29 receptors [14]. This family plays a pivotal role in immunity, inflammation and controlling cell cycle, proliferation, differentiation, and apoptosis [15]. TNFSF receptors can be divided into two different groups depending on the presence or absence of the intracellular death domain (DD) [16]. Signaling via the death domain demands the involvement of adapter proteins Fas-associated death domain (FADD) and TNF receptor-associated proteins (TRADD), leading to the activation of caspases that result in apoptotic death of a cell. The second group of TNFSF receptor signals acts only via adapter proteins termed tumor necrosis factor receptor-associated proteins (TRAFs). The DD containing receptors may use the pathway [17]. The functional activity of TNFSF receptors depends on the cellular context and the balance between pro- and antiapoptotic factors inside the cell and in the environment. Mostly, the TNFSF members are revealed on the cells of immune system and play a notable function in maintaining the equilibrium of T-cell–mediated immune responses by arranging direct signals required for the full activation of effector pool and survival of memory T cells. The TNFSF members are necessary in the development of pathogenesis of many T-cell–mediated autoimmune diseases, such as asthma, diabetes, and arthritis [16].

2.2.1 TNF-α

Tumor necrosis factor (TNF)-α is classified as homotrimeric transmembrane protein with a prominent role in systemic inflammation. Macrophages/monocytes are capable to produce TNF-α in the acute phase of inflammation, and this cytokine drives a wide range of signaling events within cells, leading to necrosis or apoptosis [17]. The TNF superfamily incorporates receptor activator of nuclear factor κB

(RANK), cluster of differentiation (CD)-40, CD27, and FAS receptor. This protein was discovered in the circulation of animals subsequent to the stimulation of their reticuloendothelial system and lipopolysaccharide (LPS) challenge. This protein has been found to provoke a rapid necrotic regression of certain forms of tumors [16].

2.2.2 Biological roles of TNF-α

Several biological functions are ascribed to the TNF-α, and for this reason, the mechanism of action is somewhat complex. Because this protein confers resistance to certain types of infections and in parallel causes pathological complications, it carries out contradictory roles. This may be connected to the varied signaling pathways that are activated. TNF-α modulates several therapeutic roles within the body, such as immunostimulation, resistance to infection agents, resistance to tumors, sleep regulation, and embryonic development [17]. On the other hand, parasitic, bacterial, and viral infections become more pathogenic or fatal due to TNF circulation. The major role of TNF is explicated as mediator in resistance against infections. Moreover, it was postulated that TNF plays a pathological role in several autoimmune diseases such as graft versus host rejection or rheumatoid arthritis. In addition, TNF exhibits antimalignant cell cytotoxicity in association with interferon. High concentrations of TNF-α are toxic to the host. The enhancement in the therapeutic index by decreasing toxicity or by increasing effectiveness is indeed needed. This may be possible through the mutations that reduce systemic cytotoxicity and increase TNF's effectiveness in selectively eliminating tumor cells. TNF-α is also implicated in physiological sleep regulation. TNF-related proteins such as receptor activator for nuclear factor κB ligand (RANKL) are required for osteoclast differentiation necessary for bone resorption [16].

2.3 IL-17 family

IL-17 is a pro-inflammatory cytokine. There are six family known members of IL-17. Also, we have just a little information of its biological functions, being the IL-17A and the IL-17F described recently [18]. IL-17–related cytokines play key roles in defense against extracellular pathogen, and their participation in the development of autoimmune diseases has drawn significant attention. Moreover, some of these molecules are involved in the amplification and perpetuation of pathological processes in many inflammatory diseases. However, the same cytokines can exert anti-inflammatory effects in specific settings, as well as play a key role in the control of immune homeostasis [19, 20].

2.4 IL-6 superfamily

IL-6 family is a group of cytokines and colony-stimulating factors (CSFs) that include IL-6, IL-27, IL-31, IL-35, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin (CT)-1, and cardiotrophin-like cytokine (CLC), among others [16, 17]. This cytokine family binds to its receptor, allowing a binding with the gp130 subunit [21, 22]. This binding allows dimerization of the subunit homogeneously or heterogeneously (either with the same subunit or cytokine receptor), creating a receptor complex. This complex allows associated proteins phosphorylation, such as Janus kinases (JAK) type 1, 2, and tyrosine kinase (TYK) 2, among others, which triggers a signaling pathway through phosphorylation toward types of signal transducer and activator of transcription (STAT) 1–6, forming another dimerization, homogeneous or

heterogeneous with other STATs, that gets into the nucleus, recognizing promoter regions and initiating the regulation of the expression of specific genes [22, 23].

In IL-6 family, there are soluble receptors that have different signaling pathways, which are mostly of inhibitory function. Although they bind to the same cytokine and to the same subunit, they transmit different signaling called trans-signaling. It is observed that these soluble receptors prolong its effect and have action on cells where cytokine emerges effect; namely, all cells reactive to IL-6 will have the soluble receptor of IL-6 (IL-6Rs) function [21, 24]. Main functions of this IL-6 family cytokines are inflammation proteins production in acute phase, B cell differentiation into antibody-forming plasma cell, T cell modulator, development of Th17, and hematopoiesis, among other functions [24–26].

2.5 Type I superfamily

Type I cytokine family, also known as hematopoietins, is made up of several types of cytokines, including IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-12, IL-15, IL-21, and granulocyte-macrophage colony-stimulating factor (GM-CSF), among others. This group of cytokines has α, β, and γ chain in common. IL-2, -4, -7, -9, -13, -15, and -21 have in common the γ chain (also known as IL2Rγ or CD132) for activation of JAK1/JAK3 and downstream STAT 1–5. While IL-3, -5, and GM-CSF share the common β chain (CSF2RB/CD131) for activation of the JAK/STAT pathway through interactions with JAK2 [3, 27], α chains do not activate signaling pathways but increase the binding affinity between the cytokine and β and γ subunit [3, 28], helping receptor specificity for gene expression [27]. While the receptor is more complex, there is more affinity of the cytokines of the receptor, which increases the signaling [27, 29]. The specificity of the receptor is conferred by α and β subunit, that in combination with γ subunit provides different stimulations. This means that the same cytokines can have different effects on the cell, depending on the receptor complexity; for example, IL-2 binds to its γ chain receptor (CD132) and β chain (IL-2Rβ), forming an intermediate affinity dimer, or also the binding of α chain (IL-2Rα), generating a high affinity. Phosphorylating tyrosine residues in JAKs, which lead to signaling to STAT5, prolonging and increasing its effect unlike the intermediate affinity [30]. Among the main functions of this cytokine family are the growth and differentiation of precursor leukocytes, as well as being modulators and initiators of the inflammatory response [3, 27].

2.6 Type II superfamily

The type II superfamily is composed of the subfamilies of interferons (IFNs) and IL-10. IFN family has the characteristic of inducing antiviral response in both hematopoietic and structural cells, serving as an essential mediator of cross talk between the immune system and host physiology during viral infections [3, 29]. This family is divided into three types INFs families: types I, II, and III.

Type I IFNs family is mainly composed of IFN-α and -β. IFN-α is expressed in leukocytes and IFN-β in fibroblasts, dendritic, and plasmacytoid cells. These IFNs have signaling pathways through JAK1 and TYK2 to phosphorylate STAT1 and STAT2 [29, 31]. These IFNs have a powerful proinflammatory effect and an antiviral response in immune and nonhematopoietic cells, as well as they can synergize with type II interferon (i.e., IFNγ) to potentiate Th1 lineage commitment by T-helper cells and cytotoxic activity by $CD8^+$ cells [3].

Type II IFNs family is composed only by IFN-γ, which is produced by active $CD4^+$ and $CD8^+$ T cells, NK cells, and macrophages by stimulation of IL-12, IL-18,

and TNF-α [3, 29, 32]. IFN-γ has signaling pathways with STAT1 through JAK1 and JAK2 [29]. IFN-γ is mediator of interaction of innate and adaptive immune cells. IFN-γ promotes B-cell differentiation toward plasma cells immunoglobulin (Ig)-G-production. Also, IFN-γ induces phagocytosis through the antimicrobial potential activation on macrophages. IFN-γ increases the expression of major histocompatibility complex (MHC) I and II, molecules in antigen-presenting cells, promotes complement activation, and increases cytotoxic activity of T cells and differentiation Th1 cell differentiation for the clearance of infectious pathogens [3, 32].

Type III INFs family is composed by IFNλ-1 (IL-29), IFNλ-2 (IL-28A), and IFNλ-3 (IL-28B) [3, 29, 32]. IFNλ-1 and -2 regulate IFN expression [3], being structurally and functionally like them by sharing beta chain but with less intensity [32]. IFNλ-3 induces antiviral response in cells through STAT1 and STAT2 [3, 33].

IL-10 is a potent pro-inflammatory cytokine, which is produced by different cells such as monocytes, macrophages, Th2, and Treg cells. The IL-10 performs its functions through the activation of the STAT1, STAT3, PI3K, and p38 mitogen-activated protein kinases (MAPK) pathways. Among its most important functions are the suppression of Th1 cytokines, the classically activated/M1 macrophage inflammatory gene expression, and the presentation of antigen [3].

3. Cytokine profile in bacterial infections

During a bacterial infection in the host, a nonspecific and immediate immune response is initiated to eliminate the pathogen, and this nonspecific response involves the recruitment of neutrophils, macrophages and dendritic cells, complement activation, and cytokine production [34]. This response can inhibit or limit microbial growth but also can cause host damage, and so it is necessary to keep this response under control; to achieve this, the host performs some strategies, including the production of cytokines. These molecules play an important role in intercellular communication and coordinate the innate and adaptive response [35].

In microbial infections, the pattern-recognition receptors (PRRs) recognize several PAMPs [36] such as DNA, double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and 5′-triphosphate RNA, as well as lipoproteins, surface glycoproteins, membrane components peptidoglycans, lipoteichoic acid (LTA), lipopolysaccharide (LPS), and glycosyl-phosphatidyl-inositol. The recognition of PAMPs by PRRs leads to the activation of NF-κB and/or MAPK [37] to produce several cytokines such as IL-1α, IL-1β, TNFα, IFN-γ, IL-12, and IL-18, being TNF-α and IL-1β the main inflammatory mediators, since they play an important role in mediating the local response through cellular activation. The inflammatory response that occurs in the presence of an infection consists of several protective effector mechanisms that promote the microbicidal functions and in turn stimulate adaptive immunity, which contributes to reduce the damage of the tissues [38] (**Figure 1**).

IL-1β is a cytokine that is inducible through the activation of PRRs such as TLRs, by microbial products or damaged cell factors [39], once the recognition of the ligands through the receptors activates the downstream signaling pathways activating the NF-κB, activator protein (AP)-1, MAPK, and type I IFNs pathways, resulting in an upregulation of inflammatory mediators, as well as chemotactic factors [40]. IL-1β is synthesized as a precursor peptide (pro-IL-1β) that is cut to generate its mature form (mIL-1β); this process involves caspase 1, and the proenzyme (procaspase-1) requires it to be cut by the inflammasome, which is a multimeric cytosolic protein complex, composed of NLR family-pyrin domain containing 3 (NALP3) and the adapter protein containing CARD (ASC) and caspase-1; once IL-1β is cut by this complex, it binds to the IL-1R1 receptor, thus initiating the signaling that induces

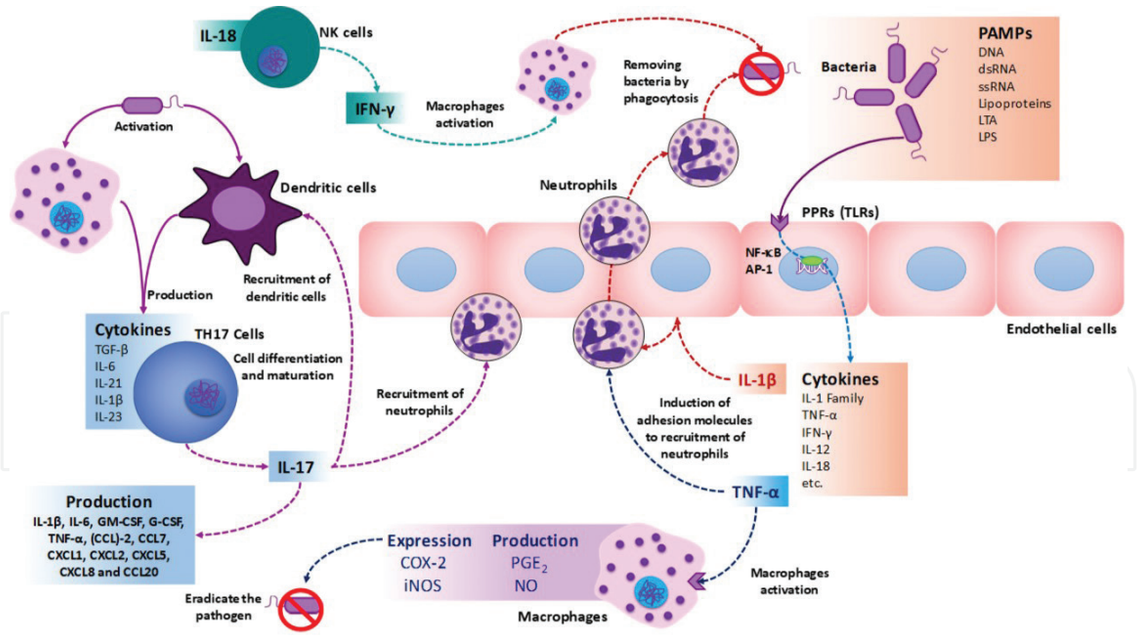

Figure 1.
Cytokines profile in bacterial infections. In response to bacterial infection, the IL-1 family cytokines, such as IL-1β, potently induces the expression of adhesion molecules in the endothelial cells and promotes the recruitment of neutrophils to the site of inflammation. TNF-α plays an important role through the recruitment of neutrophils and macrophages, besides inducing the expression of proinflammatory mediators to the site of infection. Th17 cells produce IL-17A, which induces the production of inflammatory mediators such as IL-1β, IL-6, GM-CSF, G-CSF, and TNF-α, as well as adhesion molecules. IL-18 also promotes the secretion of other proinflammatory cytokines like TNF-α, IL-1β, IL-8, and GM-CSF and consequently enhancement, migration, and activation of neutrophils during infections.

the expression of adhesion molecules in the endothelial cells and promotes the recruitment of neutrophils to the site of inflammation, as well as of the monocytes. It also has a potent stimulatory effect on phagocytosis, and it produces a chemotactic effect on leukocytes and induces the production of other inflammatory mediators of the lipid type, as well as other cytokines [41]. In vivo studies show that IL-1β is an important cytokine for the host defense against some microbial pathogens. During infection with *Staphylococcus aureus,* it was shown that the interaction of IL-1β with its receptor IL-1R plays an important role in the recruitment of neutrophils, suggesting that IL-1β is crucial for host defense against *S. aureus* and this can be transpolar to infections induced by other microorganisms [42].

Another cytokine that accompanies the IL-1β response is TNF-α, and this cytokine is produced initially during endotoxemia, as well as in response to some microbial products. TNF-α shares with IL-6 an important inflammatory property, that is, the induction of acute phase reactant protein by the liver [43]. In vivo studies show that TNF-α plays an important role in mediating clearance through the recruitment of neutrophils and macrophages to the site of infection after a bacterial intraperitoneal challenge [44], followed by an increase in the expression of COX-2, as well as inducible nitric oxide synthase (iNOS), which leads to the production of prostaglandin (PG)-E_2 and NO to eradicate the pathogen and recover homeostasis [45].

During bacterial infections, the IL-17 is another important cytokine produced. IL-17A plays an important role in the defense of the host against extracellular bacteria. The cells that are characterized mainly by producing IL-17 are a subpopulation of $CD4^+$ T cells, and their differentiation and maturation are favored by a mixture of cytokines, including transforming growth factor (TGF)-β and IL-6, IL-21 and TGF-β, or IL-1, IL-6, and IL-23 [46, 47]. The protective capacity of IL-17A against infectious agents can be mediated through several mechanisms, among these is the ability of IL-17A in the barrier surfaces to induce the production of inflammatory

mediators such as IL-1β, IL-6, GM-CSF, granulocyte colony stimulating factor (G-CSF), and TNF-α, as well as adhesion molecules. IL-17A also induces the production of chemotactic factors, such as chemokine-(C-C motif)-ligand (CCL)-2, CCL7, CXCL1, CXCL2, CXCL5, and CXCL8, responsible for recruiting neutrophils and monocytes, as well as the CCL20 that is involved in the recruitment of dendritic cells, with the aim of eliminating the extracellular pathogen [48]. In vivo and in vitro studies show that signaling through TLR4 is the main mechanism by which IL-17 is induced in response to *Klebsiella pneumoniae* infection, which induces an upregulation of granulopoietic cytokines involved in the recruitment of neutrophils [49]. In mice lacking the IL-17 receptor, the recruitment of neutrophils decreased, the bacterial load increased, and survival was compromised. Whereas overexpression of IL-17 through an adenovirus, resulted in the production of cytokines mainly, macrophage inflammatory protein (MIP)-2, G-CSF, TNF-α, and IL-1β, increasing the recruitment of neutrophils, bacterial clearance and finally survival after infection with K. pneumoniae [50]. And finally, PGE2 increases the expansion of Th17 cells in an IL-1β dependent manner, thus favoring the recruitment of these cells to the site of damage. In vitro studies show that Th17 cells in the presence of PGE_2 increase the production of CCL20, thus favoring the control of infection [51].

IL-18 also promotes the secretion of other proinflammatory cytokines like TNF-α, IL-1β, IL-8, and GM-CSF and consequently enhancement, migration, and activation of neutrophils during infections. IL-18 increases the cytotoxic activity and proliferation of $CD8^+$ T and NK cells, as well as promotes the secretion of inflammatory mediators of the type TNF-α, IL-1β, IL-8, and GM-CSF, which will activate neutrophils, thus increasing their migration [38]. During a bacterial infection, IL-18 plays an important role, since it induces IFN-γ production of NK cells [52]. The IFN-γ that is produced activates macrophages and produces cytokines that induce antimicrobial pathways against intracellular and extracellular pathogens [53]. Infection with strains of lactobacillus nonpathogenic and with streptococcus pyogenes induces the expression of IL-1β, IL-6, TNF-α, IL-12, IL-18, and IFN-γ, suggesting that this type of bacterial strains induces Th1 type cytokines [54].

4. Cytokine profile in fungal infections

As well as the response to bacteria, the response against fungi also requires coordination of the innate and adaptive immune system. The innate immune system performs its effect through the cells that have the phagocytic and antigen presenting function. These cells include neutrophils, macrophages, and dendritic cells [55]. The recognition of pathogens by the immune system involves four class of PRRs: TLRs, C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain-like (NOD-like) receptors (NLRs), and retinoic acid-inducible gene I (RIG-I) like receptors (RLRs) [56]. The CLRs, especially Dectin-1 and 2, play an important role in the pathogen recognition from *Candida spp.*; this is because the cell wall is made up of mannoproteins with O-glycosylated oligosaccharide and N-glycosylated polysaccharide moieties, with an inner layer of chitin and β (1, 3) and β (1, 6) glucans are recognized and initiate a downstream signaling through these receptors, which leads to activation of the transcription factor NF-κB and other signaling pathways that induce the production of pro-inflammatory cytokines such as IL-6, IL-1β, and IL-23 that induce the Th17 cytokines [57] (**Figure 2**).

The recognition of fungi by phagocytic cells occurs mainly through the detection of cell wall components such as mannan, β-glucan, phosphocholine, β-1,6 glucan, and even internal components such as DNA can be recognized [58, 59]. The recruitment and activation of phagocytic cells are mediated through the induction

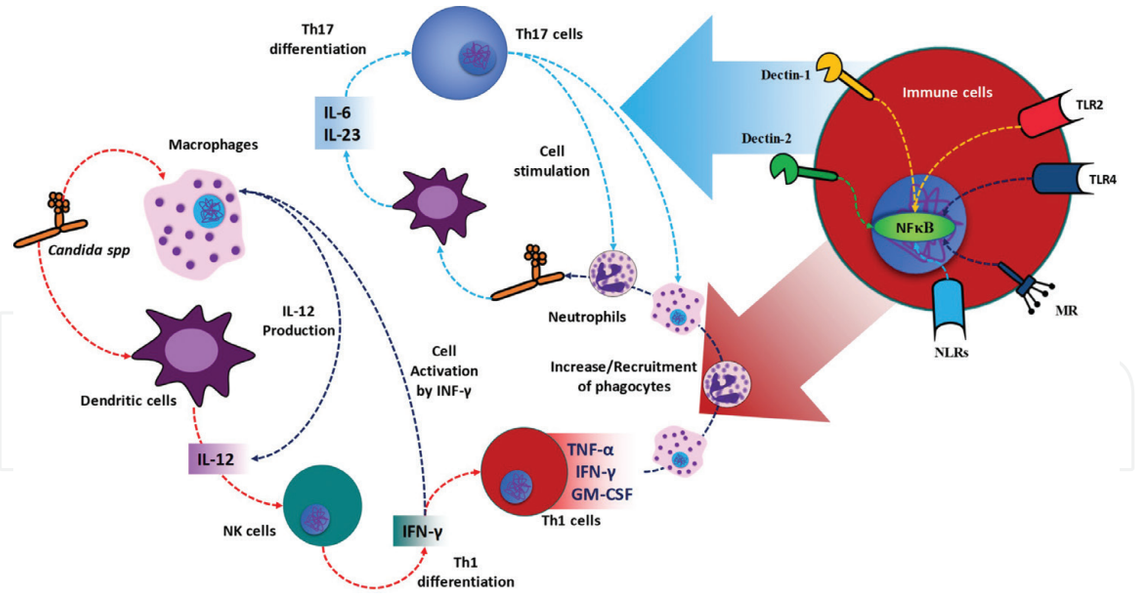

Figure 2.
Cytokines profile in fungal infections. The PRRs recognize fungal PAMPs and initiate a downstream signaling, which leads to the activation of the NF-κB and other signaling pathways inducing the production of cytokines such as IL-6, IL-1β, IL-12, TNF-α, GM-CSF, IFN-γ, and IL-23. These cytokines induce the differentiation of Th1 and Th17 immune responses against fungi infection, stimulating the migration, adherence, and phagocytosis of neutrophils and macrophages.

of proinflammatory cytokines, chemokines, and complement components. Fungi are killed by oxidative and nonoxidative mechanisms and antimicrobial peptides. These activities are influenced by the action of cytokines such as IFN-γ [59]. This cytokine produced mainly by T and NK cells stimulates the migration, adherence, and phagocytosis of neutrophils and macrophages and production of opsonizing antibodies and maintains a Th1 response as a protective response against fungi. It also induces a classical activation of macrophages that is important to stop the growth of intracellular fungal pathogens [60]. The Th1 response occurs through the release of proinflammatory cytokines IFN-γ, TNF-α, and GM-CSF, increasing the permeability in the tissue, as well as the phagocytic cells at the site of infection to efficiently clean the infection [61] (**Figure 2**).

Another important cytokine in immunity against fungi is IL-12, and this cytokine is considered the main cytokine that induces IFN-γ production. IL-12 is produced by monocytes, macrophages, and dendritic cells, in response to microbial products, and acts on NK and T cells to induce IFN-γ. On the other hand, the late secretion of IL-12 in the lymph nodes induces naive T cells to produce IFN-γ and therefore amounting a Th1 response is promoted [62]. The ability of IFN-γ to increase the production of IL-12 forms a positive feedback during the inflammatory process and the Th1 response, and this interferon in turn activates monocytes and macrophages to induce the production of IL-12 [63] (**Figure 2**). Studies in Il12p35$^{-/-}$ and IFN-γ$^{-/-}$ mice show an increase in susceptibility to infections with *Candida albicans*, and this suggests that IL-12 and the Th1 responses play an important role in controlling *Candida* infection [64]. On the other hand, neutrophils kill the extracellular and intracellular fungi through effector mechanism that includes the production of reactive oxygen and nitrogen species, as well as the release of hydrolytic enzymes and their granules containing antimicrobial peptides [65].

IL-23 is a member of the IL-12 family and plays a central role in the expansion of Th17 cells as well as their function, composed of a p19 and p40 subunit that shares it with IL-12 [66, 67]. IL-23 is produced primarily by dendritic cells, the binding of β-glucan to Dectin-1 activates the syk-CARD-9 signaling pathway leading to the production of IL-23, which promotes the Th17 response, through the differentiation

of naïve CD4+ T cells into Th17 cells and the release of IL-17A, IL-17F and IL-22 in response to infections caused by mucosal fungi [68]. These cytokines in conjunction with IL-23 have various functions in the body from a proinflammatory, anti-inflammatory, or regulatory activity, which depends on the type of microorganism, the site of infection, and the immunological status of the host (**Figure 2**). In vivo studies have shown that mice deficient of the IL-17 receptor (IL-17RA$^{-/-}$) cannot limit systemic candidiasis, as well as oropharyngeal candidiasis, being more susceptible to developing mucocutaneous candidiasis, suggesting that the Th17 lineage strongly acts through IL-17, regulating the expansion, recruitment, and migration of neutrophils, as well as CXC-chemokines and antimicrobial proteins such as β-defensin 3 [66, 69].

5. Cytokine profile in viral infections

In viral infections, the cytokines are implicated to establish an antiviral state as the unspecific first line of defense and virus-specific response. This process initiates through recognition of viral molecules by PRRs, which can be found as transmembrane receptors or in different intracellular compartment. The receptor undergoes a structural change, activating a route of signalization in the cytoplasm that end with the activation of cytoplasmic transcription factors that translocate into the nuclei to promote the expression of different cytokines. Depending of the virus and the type of cell, the type of cytokine produced may vary [70, 71].

5.1 Pattern recognition receptors versus virus

Viruses can infect virtually all cells of an organism. Epithelial, endothelial, fibroblasts, neurons, as well as innate and adaptive immune cells can be infected. PRRs are present in both nonhematopoietic origin cell and immune cells. Some PRRs recognize viral proteins, but other can detect viral single or double RNA or DNA. In human, there are 10 TLRs distributed in plasmatic membrane and endosome membranes. Of them, TLR-2 and TLR-4 can detect viral surface glycoprotein before the viral penetration. Others like TLR-3, TLR-8, and TLR-9 sense different types of viral nucleic acids in endosomes during virus entering. TLR-8 senses genomic ssRNA, TLR-3 senses dsRNA, and TLR-9 detects nonmethylated CpG viral DNA [72, 73]. Another type of receptors that sense viral RNA are the RNA helicases receptors like RIG-I and melanoma differentiation-associated gene 5 (MDA5) [71, 74]. These receptors have been demonstrated to detect viral dsRNA. This dsRNA can be genomic or an intermediate form during replication, which is formed, virtually, for all virus of single or double RNA during viral replication. However, there is evidence that some dsRNA replicative intermediators can translocate to endosomes where TLR can sense and trigger the signalization way [75].

5.2 Cytokines produced in viral infections

There are many cytokines with distinct functions. All of them are molecules with less than 20 KDa and can be pleiotropic or redundant, and also, they can synergize or antagonize each other. However, all of them are produced to ensure the virus elimination through the regulation of the immune response against the virus [76]. The process includes detection of the pathogen, signal to neighbor cells, activation and differentiation of innate immune cells, production of adhesion molecules on endothelial cell for extravasation of immune circulating cell, chemotactic molecules to attract cell to the infection foci, increase of phagocytosis, and

activation of adaptive cells to specifically eliminate infected cells and extracellular virus [77].

Cytokine network against viruses starts with some cytokines produced by virus-infected cells (**Figure 3**). Epithelial cell can produce IFN, IL-8, IL-6, IL-1, GM-CSF [78, 79], TNFα [80], IL-18 [81], IL-12 [82], IL-2 [83], and IL-23 [84, 85]. The role of these cytokines is varied, IFN induces an antiviral state, and IL-8 is a potent inflammatory attracting phagocyte cell to the site of infection. IL-1 can promote apoptosis, and it is proinflammatory and chemotactic to neutrophils. GM-CSF is a hematopoietic grow factor that recruits various immune cells to host defense [76, 86]. Moreover, in the infection course, varies cytokines are also produced by innate and adaptive cell that can also be infected or activated. In filovirus infection, IL-1β, IL-5, IL-8, and IL-18, as well as varies chemokines like MIP-1α and β, monocyte chemoattractant protein 1 (MCP-1), and IFN-γ–inducible protein 10 (IP10) among others are produced [77]. In influenza virus infection, TNF-α, IL-1 α and β, and IL-6 and IL-8 are produced [87], and hepatitis C virus can promote the expression of IL-6, IL-8, MIP-1α, and MIP-1β and IL-1 [88], while rotavirus can induce the production of IFN, IL-8, IL-6, IL-1 [89], TNF-α [80], IL-18 [81], IL-12 [82], IL-2 [83], and IL-23 [84, 85]. Thus, the infected cell can upregulate multiple cytokine genes involved in different process as activation of NK, macrophages, and dendritic cells. Increasing the production of cytokines that serve as bridge between innate and adaptive response. In the inflammation process, virus-infected cells produce and secrete proinflammatory cytokines like IL-1, IL-6, IL-8, TNF [70] and

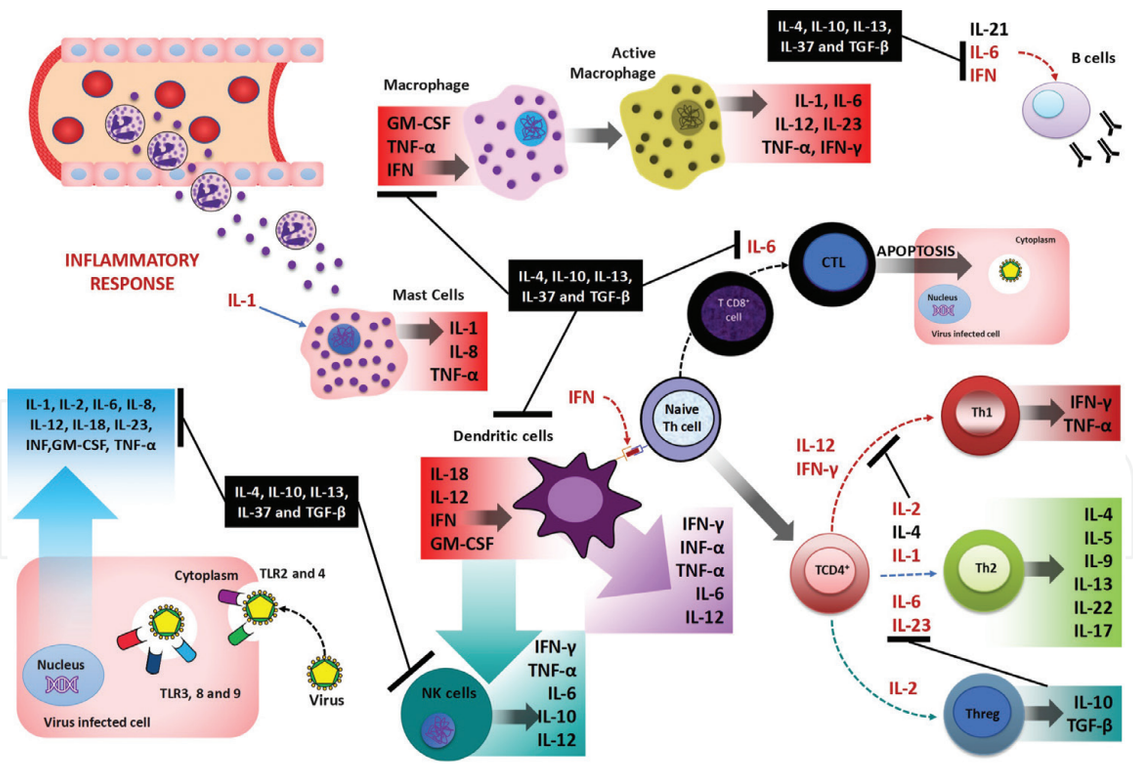

Figure 3.
Cytokines profile in viral infections. The immune response against viruses initiates through recognition of viral molecules by PRRs. These PRRs can activate a signal system culminating in the activation of transcription factors involved in the establishment of an antiviral state and an inflammation process. Cytokine network against viruses start with some cytokines produced by virus infected cells, such as IFNs, IL-8, IL-6, IL-1, GM-CSF, TNFα, IL-18, IL-12, IL-2 and IL-23, inducing a potent inflammatory response, attracting and activating phagocyte cells (e.g. neutrophils, macrophages, dendritic cells), mast cells and NK cells, to the site of infection. Furthermore, these cytokines are involved in the induction of an immune response type Th1/TCL with the purpose of eliminate infected cells and extracellular virus while cytokines such as IL-4, IL-10, IL-13, IL-37, and TGF-β modulate the immune response to a Th2 and Th17 phenotype, which produce immunomodulatory and anti-inflammatory actions.

IFN. These cytokines can be involved in the early defense of the organism. They can activate cells present in the site of infection, and they can recruit leukocyte cells from circulating system through inflammation process (**Figure 3**).

5.3 Cytokines' role in viral infection

IFN is a pleiotropic cytokine produced by virus infection. Although there are three types of IFN called type I (α/β), type II (γ) and type III (λ). Type I IFN plays an important role in control early viral infections. The role of type I IFN is to interfere with viral replication through activating the expression of antiviral molecules. Once IFN is secreted, it can act in autocrine or paracrine (like other cytokines) way, interacting with interferon receptor to induce the production of an antiviral state in the infected and noninfected neighboring cells, inhibiting different step of viral replication [76]. Also, IFN promotes the production of cytokines like IL-12, IL-6, IFN-γ, and TNF-α in innate cells including NK cells and macrophages [90]. Another function of IFN is to enhance differentiation of dendritic cells [91] and promote the antigen presentation [90] to stimulate T and B cells [92], which is redundant with the function of the IL-12 and IL-18 [93, 94]. NK cells are activated by synergism between type 1 IFNs and IL-12. However, cytokines such as IL-10, IL-6, IL-4, IL-13, and TGF-β suppress the actions of IFN, and these cytokines are known for their immunomodulatory and anti-inflammatory actions [95].

TNF-α is other pleiotropic cytokine produced by also nonhematopoietic infected cells and innate and adaptive immune cells, including macrophages, dendritic cells, natural killer, and T and B lymphocytes after being activated [96]. This cytokine can activate the production of adhesion molecules in endothelial cells and promote the extravasation of neutrophils, monocytes, and others immune cells to be attracted to infection foci. TNF also can participate in apoptosis through activating caspases. TNF-α, together with IFN-γ, acts on macrophages, inducing the production of superoxide anions and oxygen and nitrogen radicals [97]. Macrophages can also produce cytokines such as IL-1, IL-6, IL-23, IL-12, and more TNF-α [95].

IL-1 was the first interleukin to be identified and is a pleiotropic cytokine, and it acts synergically with IL-6 on the central nervous system, inducing fever by activation of the hypothalamus-pituitary-adrenal (HPA) axis [98]. This molecule also activates mast cells and induces histamine production, acting as a vasodilator, thus increases the permeability of the membrane [99]. Also, IL-1 is chemotactic factor that induces the passage of neutrophils to the site of infection. This chemotactic function is redundant with the action of IL-8, also known as chemokine CXCL8 [86] also produced by the infected cell. There are cytokines that antagonize these functions of IL-1 such as IL-10, IL-4, and IL-13 recognized for their anti-inflammatory actions [100].

Another pleiotropic cytokine is IL-18, first described as "interferon-γ-inducing factor" and member of IL-1 family. This interleukin and type I IFN are recognized by dendritic cells and trigger a signaling pathway through TRF6 and induce the expression of $CD11b^+$ in the surface of the cell [94]. These activated cells can express cytokines like IL-12, IL-6, IFN-γ, TNFα, and IFN-α, which also participates in other hematopoietic cells [101, 102]. IL-18 also participates synergistically with interleukin 12 on the activation of NK cells [93], stimulating the expression of CD25 and CD69 molecules, promoting their proliferation and cytotoxic capacity, respectively. Once activated, NK cells can induce apoptosis in virus-infected cells and produce other cytokines such as IL-12, IL-6, IL-10, IFN-γ, and TNF-α. Within the cytokines that block these functions of IL-18 are IL-37, IL-10, and TGF-β [103].

IL-6 is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis. IL-6 is an important mediator of fever and of the acute phase response, which is redundant with IL-1 and TFN-α and promotes the differentiation of cytotoxic T lymphocytes, which induce the death of infected cells by osmotic lysis [104]. IL-6 synergistically with IL-23 participates in the differentiation of Th17 [105], through the production of RORγt. Once activated, Th17 induces inflammatory response through the expression of cytokines as IL-17 and IL-22. IL-6 also promotes the proliferation of B cells by binding to a complex of receptors (gp80, CD126, and CD130) [106] and, like IL-21 [107], induces the differentiation of plasma cells stimulating the antibody production [108]. However, there exist antagonist cytokines like IL-10, IL-13, and TGF-β that inhibit all these functions of the IL-6 [103].

IL-12, also known as a T cell-stimulating factor, which together with IFN-γ, promotes differentiation of Th1 cells by activation of T-bet, and these cells can activate macrophages through expression of other cytokines like IFN and TNF, amplifying the produced immune response [109]. Although, there is evidence that viruses may selectively induce IFN production and Th1 differentiation even in the absence of IL-12 [110].

IL-2 participates in the differentiation and proliferation of Th2 (redundant with IL-4) and Treg cells by the expression of GATA-3 and FOXP3, respectively [111, 112]. Th2 cells can express IL-4, IL-5, IL-9, and IL-13, which also have pleiotropic effects in promoting type 2 effector mechanisms, such as B cells secretion of immunoglobulins, eosinophilia, mastocytosis, and M2 macrophage polarization [113]. T_{reg} cells regulate the immune response, suppressing T-cell activation [114]. T_{reg} and Th2 are known for their immunomodulatory and anti-inflammatory actions [95]. Finally, GM-CSF stimulates the generation of dendritic cells and participates in polarization of macrophages M1 [115]. Moreover, GM-CSF has also been associated with Th2 immunity and therefore M2 polarization. GM-CSF is considered a pleiotropic cytokine with inflammatory and anti-inflammatory functions [116].

6. Cytokine profile in parasitic infections

In parasitic infections is difficult to generalize about the mechanisms of antiparasitic immunity because there is a great variety of different parasites that have different morphology and reside in different locations of tissues and hosts during their life cycles [117]. In this section of the chapter, we will talk about the immune response against protozoa and helminths, two of the main parasites of medical importance for human health.

6.1 Immune system activation by parasitic protozoan infections

Protozoan parasites are much larger and more complex pathogens than viruses or bacteria and have developed additional and sophisticated strategies to escape the immune attack of the host. Currently, 30% of humans suffer parasitic protozoan infections worldwide. Life cycles of protozoans generally involve several stages of specific antigenicity, which facilitates their survival and propagation within different cells, tissues, and hosts. Frequently, the host fails to eliminate protozoan infections, which often results in a chronic disease or inapparent infections, in which the host continues to act as a reservoir of parasites [118].

The immune defense mechanisms against protozoan parasites frequently involve several immune cells such as neutrophils, macrophages, and NK cells that mediate the innate response against extracellular protozoan parasites. NK cell and

cytokine-activated macrophages are central to the innate response to intracellular parasites. Innate cytokine and dendritic cell responses also play a critical role in the induction of adaptive immunity [119].

During the initial stage of parasitic protozoan infections, intestinal epithelial cells (IECs) bind and recognize PAMPs through PRRs [120] such as TLR-2 and TLR-4 [121], which activates NF-κB and leads to the production of proinflammatory cytokines [122], including IL-1β, IL-6, IL-8, IL-12, IFN-γ, and TNF-α [123, 124], which induces the activation of a Th1 type response [125]. IFN-γ is involved in clearance of infection, through the activation of neutrophils and macrophages (**Figure 4**) [126–132]. It has been also shown that IFN-γ-producing $CD4^+$ T cells are involved protection in vaccinated mice [133]. Several studies suggest a role for IFN-γ in the pathogenesis of parasitic protozoan infections. In both humans and animal models, the production of high levels of IFN-γ is associated with resistance to infection [134–136], while low levels of IFN-γ are associated with an increased susceptibility to infection. Therefore, it is considered highly probable that IFN-γ provides protection against infection by activation of neutrophils and/or macrophages [125]. The production of reactive oxygen species (ROS) and NO through the complex of NADPH oxidase and iNOS, respectively, plays a critical role in the elimination of protozoan parasites [131, 132]. In experimental studies, infection protection was mediated by IFN-γ from NK T cells (NKT), while TNF-α is produced by increased tissue damage [137, 138], together with IL-1 and IL-8 [139] (**Figure 4**).

On the other hand, the antigenic exposure of protozoan parasites activates a Th2-type immune response by the host, inducing the production of anti-inflammatory cytokines such as IL-4, IL-10 [125], IL-5 and IL-13, which try to attenuate the Th1 type response characterized also by the INF-γ production, leading to upregulation of Th2 cytokine responses (IL-4, IL-5, and IL-13) and Th17 (IL-17), suppressing the production of Th1 cytokines [140] (**Figure 4**). In addition, another cytokine of anti-inflammatory importance is TGF-β, which acts in a synergistic manner to counteract this Th1 type response, activating macrophages which produce

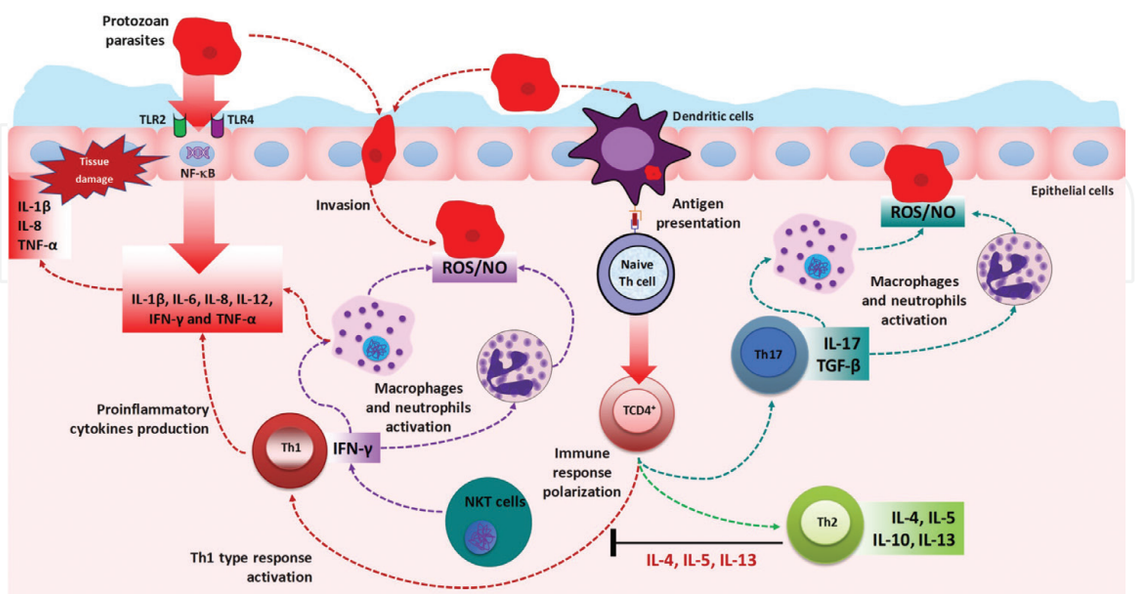

Figure 4.
Cytokines profile in parasitic protozoan infections. The immune defense mechanisms against protozoan parasites involve several immune cells such as neutrophils, macrophages, NK cells, and $CD4^+$ T cells. These cells are capable to produce proinflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-12, IFN-γ, and TNF-α, promoting type 1 immune response. Likewise, protozoan parasites activate a Th2-type immune response, producing anti-inflammatory cytokines such as IL-4, IL-10, IL-5, and IL-13, suppressing the production of Th1 cytokines.

NO, through iNOS, for the elimination of the parasite [138]. Therefore, Th1-type cytokine response is characterized mainly by the production of IFN-γ, whereas susceptibility to tissue damage by protozoan parasites is critically dependent on a Th2-type cytokine response mediated mainly by IL-4.

6.2 Immune system activation by parasitic helminth infection

More than two billion people around the world are infected with helminth parasites. Parasitic helminth infections are a major public health problem worldwide due to their ability to cause great morbidity and socioeconomic loss [141, 142].

The immune response against helminth parasites is characterized by the induction of an early Th1-type immune response, with the subsequent predominance of a Th2 type immune response, resulting in a mixture of both Th1/Th2 immune responses [143, 144], which depend on the $CD4^+$ T cells [145]. The $CD4^+$ T cells have a key role in the establishment of the cytokine environment during helminth parasite infection, thus directing their differentiation either by suppressing or favoring the inflammatory response at the intestinal level, which is crucial for the elimination of the parasite [146] (**Figure 5**).

PAMPs derived from helminth parasites induce the activation and maturation of dendritic cells [147, 148], promoting the development of the Th1 immune response [149], which results in a significant increase of Th1 cytokines such as IL-12 [150–152], INF-γ [149–153], IL-1β [152, 154], and TNF-α [150–152, 155] (**Figure 5**). However, in recent years, several studies have shown that this immune response of Th1 type favors infection by helminth parasites. On the one hand, IL-12 and INF-γ are two important cytokines against infection by helminth parasites, since they participate in the polarization of the Th1 type immune response [149–151, 153]. However, exogenous IL-12 is capable of suppressing intestinal mastocytosis, delaying the parasite expulsion, and increasing the parasite burden at the muscular level [156]. INF-γ induces the expression of iNOS, activates transcription factors such as NF-κB [157], and regulates the production of pro-inflammatory cytokines such as TNF-α [158]. Studies have shown that TNF-α is a cytokine that is produced during

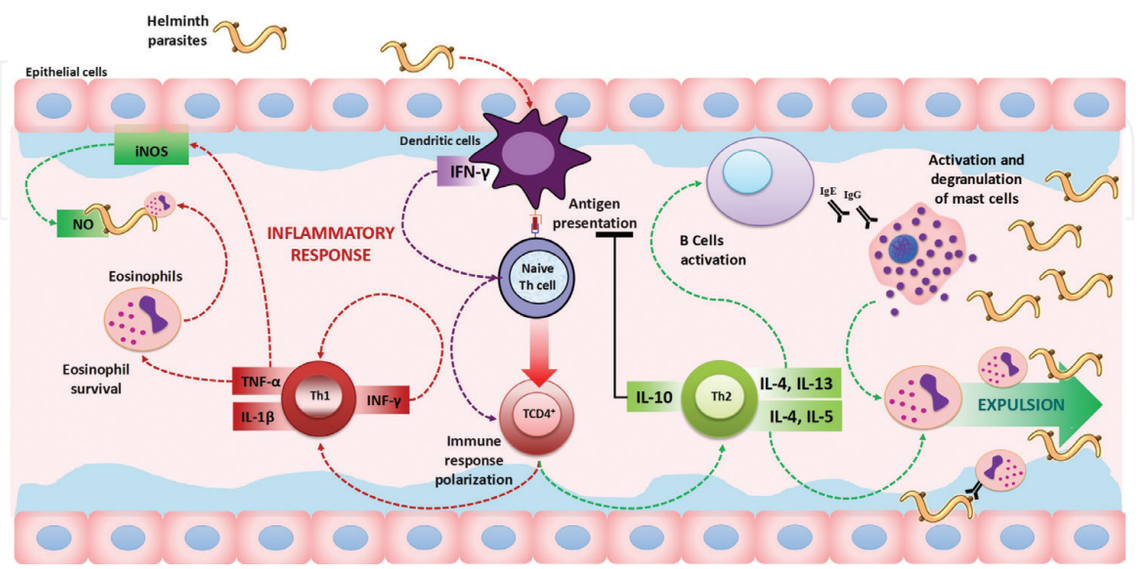

Figure 5.
Cytokines profile in parasitic helminth infection. The immune response against helminth parasites is characterized by the induction of an early Th1 type immune response, which results in a significant increase of Th1 cytokines such as IL-12, INF-γ, IL-1β, and TNF-α. Then, there is a subsequent predominance of a Th2 type immune response characterized by the release of IL-4, IL-5, IL-10, and IL-13 favoring helminth parasites expulsion.

intestinal infection by helminth parasites [150, 151, 159], which is necessary in the protection against the parasite through the Th2 immune response [160]. However, several studies have associated the production of TNF-α with the development of intestinal pathology during infection by helminth parasites [155, 161, 162]. One of the effects of TNF-α is the iNOS expression and consequently the NO production [163–165]. Helminth parasite antigens are capable to induce the expression of iNOS, with the subsequent production of NO [166], which acts mainly as an effector molecule against both extracellular and intracellular parasites [167]. Studies in iNOS knockout mice infected with helminth parasites, showed a reduction in the expression of Th2 cytokines (IL-4, IL-5), a reduced humoral response (IgG and IgE), with a decrease in mastocytosis. However, no significant difference was observed in the helminth parasite expulsion, although iNOS knockout mice showed a decrease in intestinal pathology compared to wild-type animals. These results suggest that NO is not required for the helminth parasite expulsion, but its production is responsible for the intestinal pathology [155, 168]. With respect to IL-1β, it is well known that it participates in the intestinal inflammatory response in the helminth parasites infection, observing high levels during intestinal infection. However, until now, the role of IL-1β is not well understood [159].

With respect to the Th2 type immune response, in vitro studies have shown that helminth parasite antigens are capable of dendritic cells activating, inducing the synthesis of Th2 cytokines such as IL-4, IL-5, IL-10, and IL-13 [147, 149, 153, 169]. Likewise, studies in in vivo models have shown that helminth parasites infection is a significant increase in the synthesis of IL-4, IL-5, IL-10, and IL-13 [150, 151, 159, 170] (**Figure 5**). IL-10 may suppress antigen presentation by dendritic cells and inhibition of IL-12 secretion. In addition, helminth parasite antigens increased both IL-4 and IL-10 production derived from Th2 cells with a decrease in INF-γ production, polarizing the immune response to a strong Th2 cellular immune response, protective and responsible for the helminth parasite expulsion [143]. IL-10 is a Th2 cytokine, which is necessary for a successful intestinal immune response. This is because the absence or decrease of IL-10 causes a significant delay in the helminth parasite expulsion and an increase in the parasite burden [171]. IL-4 and IL-13 induce muscle cells hypercontractility of the jejunum and intestinal mastocytosis, promoting the helminth parasite expulsion [161, 172]. In IL-4/IL-13 mice deficient, a reduction in the helminth parasite expulsion, mastocytosis, and development of intestinal pathology was observed [161, 162, 173, 174]. Therefore, these studies suggest that IL-4 and IL-13 can regulate the induction of the protective Th2 immune response and intestinal inflammation, both associated with the helminth parasite expulsion [162]. During the Th2 immune response, the cytokines such as IL-4, IL-5, and IL-13 stimulate IgE synthesis [175], inducing mast cell and eosinophil hyperplasia [176], triggering immediate hypersensitivity reactions, and promoting the helminth parasite expulsion from the intestine [177]. However, mast cells and eosinophils are involved in tissue damage, thus promoting the inflammatory response. It suggests that the protective role of the Th2 type immune response is not sufficient facing the challenge against helminth parasite infections, as it contributes to the development of immunopathology [178] (**Figure 5**).

7. Conclusion

Although cytokines are produced with the purpose of modulating the immune response against infections caused by microorganisms, such as bacteria, fungi, viruses, and parasites, there is evidence that these microorganisms can induce cytokine production with bad prognostic to host recovery. In this sense, overproduction

of inflammatory cytokines may be responsible for the severe damage observed in many microorganism infections. For this reason, a better understanding over the cytokine balance related to diseases by microorganisms is required to avoid severe damage against the organism caused by overreaction of the immune system.

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Conflict of interest

We have no conflict of interest related to this work.

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