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Cytokines and Interferons: Types and Functions

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Abstract

This chapter aims to describe and review the main important cytokines types (notably interferons), including their biological activities, functions and structures. As a high number of molecules are available, synthesis of the most important cytokines, including tumor factor necrosis, interferons and interleukins will be presented. Here we also describe the relationships between those cytokines with some autoimmune diseases that are promoted by them.

Keywords: biological function, cytokines, interferon, tumor factor necrosis, interleukins

1. Introduction

Cytokines are a cell-signaling group of low molecular weight extracellular polypeptides/glycoproteins synthesized by different immune cells, mainly, by T cells, neutrophils and macrophages, which are responsible to promote and regulate immune response (i.e. activity, differentiation, proliferation and production of cells and other cytokines). These polypeptides act on signaling molecules and cells, stimulating them toward sites of inflammation, infections, traumas, acting on primary lymphocyte growth factors and other biological functions. Cytokines may act in the site where they are produced (autocrine action), in nearby cells (paracrine action) or in distant cells (endocrine action). In this sense, they are important in the development and regulation of immune system cells. Different types of cytokines had been discovered, including chemokines, interferons (IFN), interleukins (IL), lymphokines and tumor necrosis factor (TNF) [1–4].

In this chapter, we describe and review different cytokines. They will be categorized according to their type, followed by presentation of their function and a brief scope: IFN (IFN-α, β and γ), IL (IL-1, IL-2 and others), TNF (TNF-α and TNF-β) and others. A brief explanation of different cytokines activities also will be done, comprising pro- and anti-inflammatory action, cellular immune responses and performance in hematopoiesis. Methods to reach these objectives include a literature search in the most relevant sources of information, including PubMed/Medline, Scopus and Web of Science databases.

As key results, this chapter will provide a better understanding on cytokines types and functions, with organized concepts about this subject. As we aim to provide a comprehensive review of the available data regarding cytokines, this chapter will be a valuable source of information for readers who seek a thorough and structured synthesis on this topic.

2. Interferons

Interferon family represents a widely expressed group of cytokines. It includes three main classes, designated as type I IFNs, type II IFN and type III IFNs. The two main type I IFNs includes IFN-α (further classified into 13 different subtypes such as IFN-α1, -α2, -α4, -α5, -α6, -α7, -α8, -α10, -α13, -α14, -α16, -α17 and -α21), and IFN-β. The term *interferon* derives from the ability of these cytokines to interfere with viral replication. Type I IFNs present a potent antiviral effect by inhibiting viral replication, increasing the lysis potential of natural killer (NK) cells and the expression of MHC class I molecules on virus-infected cells, and stimulating the development of Th1 cells. During an infectious process, this type of interferon becomes abundant and is easily detectable in the blood. On the other hand, type II IFN has only one representative, IFN-γ. This cytokine plays a major role is macrophage activation both in innate and adaptive immune responses. Type III IFNs, also denoted IL-28/29, present similar biological effects to type I IFN, playing an important role in host defense against viral infections [5–8].

2.1. History

Interferon was the first described member of the class of protein molecules now known as cytokines. Nowadays, interferons are well known to participate in innate immune system, mediating responses against viral infections. This role of the IFNs was first described in the 1930s, when a research conducted by Hoskins demonstrated that rabbits previously infected by the herpes simplex virus were protected against subsequent infections by the same type of virus. In 1937, a few years after Hoskins' experiment, Findlay and MacCallum showed that the virus-infected animals were also resistant to infections caused by antigenically different viruses, corroborating and complementing the existing evidence regarding IFNs functions at that time. Their findings, however, were only confirmed in 1957, when Isaacs and Lindenmann, through cell cultures research, demonstrated that cells infected by a virus had the ability to produce a protein that could make other cells resistant to other viruses. Glasgow, in 1966, theorized that the interferon production was not limited to primary infection by viruses, and that this cytokine might play a role following re-infection. Therefore, the concept of "immune

induction" of interferon became well established by the end of the 1960s. The early 1970s were marked by two milestone studies, which confirmed the existence of two different categories of interferons, which differed physicochemically and biologically: the immune-induced interferon (currently known as type II IFN) and the classical virus-induced interferon (currently known as type I IFN). In 1980, the terms IFN-α and IFN-β arose to designate the "classical interferons", which had been obtained in pure forms exhibiting homogeneity. Albeit the "immune-induced interferon" had not been obtained in pure form at that time, it was recognized that this molecule was different from IFN-α and IFN-β, being, therefore, designated as IFN-γ. Despite the markedly difference of this cytokine when compared to IFN-α and IFN-β, IFN-γ was originally classified in the IFN family due to its ability to 'interfere' with viral infections, which characterizes the original definition of IFNs. In the last decade, a third type of IFN (type III IFN) has been described, the IFN-λ. This type is also referred as interleukins IL-28A and B (IFN-λ2 and IFN-λ3, respectively), and IL-29 (IFN-λ1) [8–11].

2.2. Pathways of induction and major roles of interferons

There are several isotypes of type I IFNs. In humans, there are multiple forms of IFN-α, only one type of IFN-β and additional isotypes, as IFN-δ, IFN-ϵ, IFN-κ, IFN-τ and IFN-ω (IFN-δ and IFN-τ have been only described in pigs and cattle). This sort of cytokines presents similar structure, binding to the same cell surface receptor, and they are coded by a family of linked genes located on the human chromosome 9 [7, 12].

Type I IFN synthesis is induced by microbial challenge (i.e., viral and bacterial infections or microbial nucleic acids exposure) when the pattern recognition receptors (PRRs) sense these microorganisms. These receptors can be found in the cytosol or in the endosome. Once a virus infects a cell, the cell activates signals that lead to phosphorylation, dimerization and passage to the nucleus of the interferon response factor 3 (IRF3). Along with IRF3, other transcription factors, such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), activate the transcription of IFN-β gene. After this process, secreted IFN-β binds to the interferon receptor (IFNAR) on the surface of the infected cell, producing an autocrine signaling to mobilize other interferon response factors and alter gene expression patterns to provide interferon response. Besides autocrine signaling, IFN-β also binds to the interferon receptor expressed by neighboring non-virus infected cells, acting in a paracrine manner to promote interferon response in order to help these cells to resist viral infection [5, 13, 14].

Interferon response comprises a series of reactions that alter the expression of a variety of human genes. These reactions are mediated by the binding with type I interferon receptors, which consists of the IFNAR1 and IFNAR2 transmembrane proteins, and two associated cytoplasmic tyrosine kinases, the Janus kinase 1 (Jak1) and tyrosine kinase 2 (TyK2). In addition to IRF3, another transcription factor induced by interferon response is interferon response factor 7 (IRF7), which is responsible to initiate IFN-α transcription without the need of NF-κB and AP-1. The canonical pathway that mediates the biological effects of IFNs corresponds to the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Both the antiviral and inflammatory effects of IFN-α/IFN-β are specifically mediated by STAT1 and STAT2. This pathway, however, does not work in isolated manner. It extensively communicates with

other signal transduction pathways, therefore recruiting several effector molecules to promote a potent effect against viral infections, antiproliferative and antitumor activities, in addition to the immunomodulatory effects. In healthy individuals, these type I IFN genes are strictly regulated, with almost no constitutive IFN-α production [7, 15, 16].

A high number of cells produce IFN-α and IFN-β, including macrophages, fibroblasts, and endothelial cells, specialized leukocytes, called interferon-producing cells (IPCs), or natural interferon-producing cells, secrete up to 1000 times more interferon than the others after microbial challenge. These cells, also known as plasmacytoid dendritic cell (pDCs), are present in the blood, comprising less than 1% of the total peripheral blood mononuclear cells. In terms of morphology, they are similar to plasmocytes, another type of cell responsible for the massive production of this cytokine. IPCs express toll-like receptors (TLRs) 6, 7, 9 and 10, which are critical components of innate immunity, acting as pathogen sensors. Toll-like receptors act on innate immunity cells by detecting conserved patterns of pathogenic microorganisms. These cells, when activated by these receptors, lead to maturation of antigen-presenting cells and production of inflammatory cytokines. Hence, IPCs become responsive to a variety of viral infections through quick secretion of massive amounts of type I IFN. In other words, these cells can produce substantial amounts of type I IFN in response to stimulation with a wide range of DNA and RNA viruses, which signal through TLR9 and TLR7, respectively. During an antiviral immune response, therefore, IPCs are able to promote the function of NK cells, B and T cells, and myeloid dendritic cells through type I IFN. IPCs still differentiate into a unique type of mature dendritic cell, which allows the direct regulation of the function of T cells and links innate and adaptive immune responses. This process occurs at a later stage of viral infection [11, 17–20].

The whole process mentioned above can be summarized through the following explanation. On the first day after stimulation by viral infection (microbial challenge), IPCs produce massive amounts of type I IFN. On the following 2 days, IPCs differentiate into a type of dendritic cell called a plasmacytoid dendritic cell, which maintains the ability to produce interferon. During the infection process, these cells cluster into the T cell areas of the draining lymph nodes. Although there is some similarity between plasmacytoid dendritic cells and myeloid dendritic cells (known as conventional dendritic cells), it is believed that plasmacytoid dendritic cells do not have a substantial involvement in T cell activation in adaptive immunity, which is the main function of conventional dendritic cells. Therefore, in the context of innate immunity, conventional dendritic cells produce relatively small amounts of type I IFN, but produce large amounts of IL-12, a cytokine that interacts with type I IFN to activate the NK cell response to viral infection [7, 11].

IFNs, besides being first line of defense against viral infections, play important roles in immunosurveillance for malignant cells. More specifically, type I interferons present a potent antiviral activity, which is associated with several physiological changes. For ease of understanding, the role of type I interferons, in which IFN-α and IFN-β are the major actors, can be divided in three main functions. Firstly, these cytokines stimulate resistance to viral replication in all cells through cellular genes activation, with the consequent destruction of the viral mRNA and inhibition of the viral proteins translation. Secondly, they promote an increase in

ligands to NK cell receptors expression in virus-infected cells. Thirdly, they lead to NK cells to eradicate virus-infected cells [8, 21, 22].

NK cells are lymphocytes of innate immune system, which provide defense against viral infections by secreting cytokines (mainly IFN-γ) and killing infected cells. When IFN-α or IFN-β bind to interferon receptors on circulating NK cells, these are activated and directed to infected tissues, where they attack virus-infected cells. It is possible to say that NK cells play, in innate immune response, similar functions than cytotoxic T cells in adaptive immune response [23, 24].

Type II and type III IFNs do not share homogeneity with type I IFN in terms of induction, and the signaling pathways are, therefore, through their own receptors. Nevertheless, the signal pathways involved with type I IFN and type II IFN, as well as the target genes used by these cytokines, somewhat overlap. IFN-γ receptor (IFNGR) is composed by two structurally homologous polypeptides that belong to the type II cytokine receptor family, named IFN-γR1 and IFN-γR2. IFN-γ (originally designated as macrophage-activating factor) binds and induces dimerization of the two receptor chains. This process leads to the activation of JAK1 and JAK2 kinases and, subsequently, to the phosphorylation and dimerization of STAT1, which stimulates the transcription of several genes. The genes induced by this cytokine encode several different molecules that mediate the biological activities of IFN-γ [5, 14, 25].

Unlike IFN-α or IFN-β, the gene that encodes IFN-γ is located on the human chromosome 12. This unique specimen of type II IFN is the primary cytokine involved in macrophage activation (named as classical activation) and plays a critical role in immunity against intracellular microorganisms. In innate immune system, IFN-γ is the main cytokine produced by NK cells, acting as a mediator of innate immunity. Despite belonging to the *interferon* family, IFN-γ does not produce a potent antiviral effect, running primarily as an activator of effector cells of the immune system. In adaptive immunity, IFN-γ is produced by T cells in response to antigen recognition, and its secretion is increased by IL-12 and IL-18. In addition, B cells and professional antigen-presenting cells (e.g., monocyte/macrophage and dendritic cells) are also involved in this cytokine production. While IL-12 and IL-18 control the production of IFN-γ by promoting its synthesis, IL-4 and IL-10 correspond to the negative regulators of type II IFN production [5, 8, 25].

Regarding biological activities, both type I and type II IFN are essential in the immediate cellular response to viral infections. IFN-γ acts on immune cell activation and induction of the major histocompatibility complex (MHC) molecules, which is important at a later stage of the response. Thus, this cytokine establishes an antiviral state for long-term control, coordinating the transition from innate to adaptive immunity. IFN-γ plays a role in macrophage activation, triggering microbicide effector functions in these cells. Macrophages activated by IFN-γ promote more intensive pinocytosis and phagocytosis, in addition to an improved microbial killing ability. Furthermore, IFN-γ acts as a cell growth inhibitor and presents the ability of triggering apoptosis [25, 26].

In summary, in the early stages of infection, NK cells are the main producers of IFN-γ, whose major role is macrophage activation. Once activated, macrophages release cytokines

that participate in T cells activation, therefore initiating the adaptive immune response. After being produced and entering the infected site, the effector T cells become, in turn, the main source of IFN-γ and cell-mediated cytotoxicity. Besides the effects on host defense, IFN-γ is also involved in the protection against tumor development [5, 26].

Type III IFN (IL-28/29 or IFN-λ), likewise type I IFN, present antiviral activity. Type III IFN is subdivided in IFN-λ1 and IFN-λ2/3, which are expressed in identical patterns. The signaling pathway related to IFN-λ is similar to IFN-α/IFN-β, involving mechanisms relying on IRFs and NF-κB actions, with the last one playing an essential role in regulating type III IFN expression. Nevertheless, the expression of IFN-λ is more flexible when compared to type I IFN, once it also involves independent actions of NF-kB and IRFs, allowing the production of this cytokine in response to a wider range of stimuli. Most classes of virus and some bacterial products induce IFN-λ expression, and almost all cell types, mostly pDCs, produce type III IFN after virus infection. However, different from the other types of IFN, macrophages are not involved in IFN-λ expression. Regarding biological activities, IFN-λ acts as the first line in host defense against viral infections, besides regulating innate and adaptive immune responses. Recently, a new member of the Interferon Lambda family was identified, the IFN-λ4. This cytokine presents strong antiviral activity and has been recently described to be related to hepatitis C treatment failure. Several *in vivo* studies have shown that IFN-λ can be developed as a potent antiviral agent, covering a wide spectrum of viral infections, with the additional benefit of not promoting the unwanted pro-inflammatory effects of IFN-α [6, 27–29].

2.3. Interferons and related diseases

The first sign that type I IFN was somehow involved with human autoimmune diseases came from the observation of an increased incidence of autoantibodies and autoimmune diseases after type I IFN treatment. Hence, when considering the indication of IFN-α therapy for some conditions (e.g., hepatitis C virus infection), it is important to scrutinize the presence of autoantibodies in the patient, since they may increase the risk for autoimmune disease development with this kind of treatment [14]. As previously mentioned, pDCs are responsible for producing high levels of type I IFN in response to nucleic acid-containing immune complexes through the activation of TLRs 7 and 9 [11]. These immune complexes are prevalent in autoimmune conditions, such as systemic lupus erythematosus (SLE), which makes this process highly relevant for the development of autoimmunity. It has been described that, in autoimmune diseases, several key immune effector cells, such as B cells, T effector cells and regulatory T cells are modulated by IFN-α. Hence, type I IFN plays a substantial role in this kind of condition [16].

Regarding type II IFN, IFN-γ may contribute to the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis and type I diabetes mellitus. The role of this cytokine in autoimmune diseases (both in promoting and suppressing the condition) has been shown in several mouse models. The administration of IFN-γ at very early stages of experimental autoimmune encephalomyelitis exacerbates the disease, while its administration at a later stage reduces disease severity. Hence, the absence of biomarkers that could indicate the best stage of the disease to initiate IFN-γ treatment consists in a limiting factor for its therapeutic use [25, 26, 30]. This subject will be reported in the topic "Cytokines and autoantibodies".

Due to the ability to increase immune response, type I and type II IFN have been explored in clinical trials as treatments for several conditions. It has been found that these cytokines are involved with the improvement of several conditions, such as hepatitis B and C virus infections, autoimmune diseases and certain types of leukemia and lymphomas. Hence, this class of cytokines, which play a paramount role in the immune system, consist of valuable treatment strategy. Still, in order to obtain full advantage of the therapeutic potential of interferons, further researches are needed to elucidate the core mechanisms of their effects [31, 32].

3. Tumor necrosis factor

Tumor necrosis factor (TNF) is a cytokine that had the name derived from it discovery in 1975 as a molecule that caused in vitro necrosis of tumors. Shortly thereafter, it was observed that TNF expression was promoted by immune system cells. These discoveries were important to a posterior characterizing of the TNF superfamily and the TNF receptor superfamily, which has more than 40 members, being the most outstanding TNF-α (commonly named as TNF) and TNF-β (also named Iymphotoxin), but also including cytokines and membrane proteins that have similar sequence homologies and a homotrimeric pyramidal structure (e.g. CD40 ligand, FAS ligand, OX40 ligand, GITR ligand and other several proteins). The binding of this family of cytokines with their respective receptors triggers especially inflammatory reactions [33–37] .

TNF-β, a type II transmembrane protein, is an important key in the development of lymph nodes and Peyer's patches, and also for the maintenance of secondary lymphoid organs. The expression of TNF-β is mainly stimulated by lymphocytes. TNF-α will be better described in the following topics [38, 39].

Although it were discovered many receptors along the decades, two are best known: TNFR1 (55 kD) and TNFR2 (75 kD). Both receptors are plasma membrane trimmers, while TNFR1 is expressed by most human cells and TNFR2 is mainly produced by immune system cells. It is important to mention that TNFR2 have a higher affinity to TNF. They are related to inflammatory reactions, so that a cytokine bind to the receptor, it induces the recruitment of proteins that are important for the process [35, 40] .

3.1. Expression and structure of tumor necrosis factor alpha

The production of this cytokine is performed by different cells from the immune system, which includes T cells, NK cells, macrophages and monocytes. The stimulus for TNF expression includes different factors, such as bind to pathogen lipopolysaccharide (LPS) and other parts with toll-like receptors (TLRs), and also by other cytokines, highlighting IFN-y [33, 35].

It is primary secreted as a nonglycosylated type II membrane protein arranged as homotrimer. TNF membrane releases a trimeric soluble cytokine (a polypeptide that weighs around 17-kDa with triangular pyramid shape) through proteolytic cleavage by metalloprotease TNF-converting enzyme, and this is the circulating form that is found in blood plasma, and that allows a potent capacity to displacement in the body, thus it endocrine function. It is not

well defined but from three of these circulating TNF it is possible to polymerize them forming one 51-kD polypeptide which facilitates the binding of the cytokine with three receptors simultaneously [37, 41, 42].

3.2. Tumor necrosis factor alpha biologic functions

TNF have a lot of physiologic multifunction including immune and inflammatory roles and the survival and death of different cells. The main function of cytokine is to attract and activate immune cells to sites of infections and to destroy pathogens, such as bacteria and virus. In this context, TNF stimulate vascular endothelial cells to express adhesion molecules (e.g. selectins and ligands for leukocyte integrins) that allows immune system cells to connect the wall of blood vessels. Additionally, complementing the inflammatory response, TNF induces the production of chemokines that increase the affinity of leukocyte to their ligands, the expression of IL-1 and to activate microbicidal functions of immune system cells. For all TNF importance in the inflammatory reaction, if low quantities of this cytokine are presented in the local, the containment of the infection may be impaired [33, 37, 41–43].

TNF is also well known to act in inflammatory reaction of some autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease. Errors in this production are responsible for a considerable number of autoimmune, neoplastic and other diseases. Under these conditions, the treatment of these diseases are based on biologic agents targeting TNF, and thus looking for reducing the number of available TNF molecules or to block it receptors [33, 35, 40].

TNF also promotes necrosis of tumor cells by inducing programmed cell death, a cytolytic potential. The activation of apoptosis mechanism is mediated by TNFR1, by stimulating the recruitment of death signaling proteins, such as Fas-associated protein with death, TNFR-associated factor (TRAF)-1 and TNFR-associated death domain protein (TRADD). These intracellular proteins are responsible for the release of other proteins such as pro-caspase-8, which in it activated form activate caspase-3, caspase-6, caspase-7 and other cytosolic substrates. These proteins induce genomic DNA degradation and cell death through interacting with latent DNAse. Evidences also suggest that TNF have the capacity to induce carcinogenesis and to stabilize tumors, an event that it is opposite of the previous explained, by DNA mutations and it mechanism of repair (i.e. genotoxic potential). This is possible due to the activation of NF-κB in tumor cells and by promoting production of IL-6 (a tumor-promoting cytokine), both facilitate metastasis and cancer cells to escape from immune system defense [35, 40–42].

There are other biological events and actions caused by TNF. When this cytokine is produced in large scale, such as in severe infection, it may induce shock or decrease of blood pressure due to reducing vascular muscle tone and myocardial contractility. Additionally, in high concentrations TNF can reduce blood glucose concentration, and cause intravascular thrombosis (by decreasing anticoagulant capabilities of the endothelium). TNF is also known as an endogenous pyrogen because it promotes fever by stimulating hypothalamus cells to produce prostaglandins [33, 40].

4. Interleukins

Interleukins (ILs) are a group of secreted proteins with diverse structures and functions. These proteins bind to receptors and are involved in the communication between leukocytes. They are intimately related with activation and suppression of the immune system and cell division. The interleukins are synthesized mostly by helper CD4$^+$ T lymphocytes, monocytes, macrophages and endothelial cells [5, 44, 45].

Interleukins are named as IL plus a number. Previously, different names were used to refer to the same IL. For instance, IL-1 was called lymphocyte-activating factor, mitogenic protein or T cell replacing factor III. In order to standardize the nomenclature, in 1979, during the Second International Lymphokine Workshop, the term interleukin was introduced. After that, the interleukins started being named consecutively according to the date of their discovery [44, 46, 47].

There have been identified 40 interleukins so far and some of them are further divided into subtypes (e.g. IL-1α, IL-1β). These ILs are grouped in families based on sequence homology and receptor chain similarities or functional properties [5, 44, 48, 49].

In this section, a brief description of various ILs will be presented. Focus will be given to the families of interleukins 1 and 2.

4.1. The interleukin-1 family

Interleukin-1 family is composed by 11 cytokines: 7 ligands with agonist activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ), 3 receptor antagonists (IL-1Ra, IL-36Ra and IL-38) and 1 anti-inflammatory cytokine (IL-37) [44, 50].

The interleukin-1 family started with only two components: IL-1α, IL-1β. Over the years, new IL with similar behavior and/or structure were discovered and added to the family. All the agonists members of this family show pro-inflammatory activity. These cytokines share a common C-terminal three-dimensional structure with a typical β-trefoil fold consisting of 12-β-strands connected by 11 loops, and have identical positioning of certain introns. Considering that, it is plausible to affirm that they probably arose from the duplication of a common ancestral gene [45, 51, 52].

All members of the family except IL-18 and IL-33 have genes encoding on chromosome 2 in a 400 kb region in human species. Despite the fact that all the cytokines are extracellular, they are synthesized without a hydrophobic leader sequence and are not secreted via reticulum endoplasmic-Golgi pathway, with the exception of IL-1Ra. The secretion mechanism of the other members of the family is still not known. These cytokines bind to closely related receptors, and many of the encoding genes are clustered in a short region of chromosome 2. The receptors contain extracellular immunoglobulin domains and a toll/IL-1 receptor (TIR) domain in the cytoplasmic portion [45, 52].

In order to become active, both IL-1α and IL-1β bind to the ligand-binding chain type I (IL-1R1). Then, the co-receptor, termed the accessory protein (IL-1RAcP), is recruited, and together they

form a heterodimeric complex. The signaling that will culminate in a variety of inflammatory activities is initiated by the recruitment of the adaptor protein MyD88 to the toll-IL-1 receptor (TIR), which is followed by the phosphorylation of kinases, the translocation of the nuclear factor kappa B (NF-κB) to the nucleus and the expression of inflammatory genes [50, 51].

Both IL-1α and IL-1β have precursor forms. The precursor of IL-1α is present in the epithelial layers of the gastrointestinal tract, lung, liver, kidney, endothelial cells and astrocytes; and it is capable of binding to the IL-1R1 and initiating the signaling cascade, essentially after cell death by necrosis (e.g. myocardial infarction and stroke). On the other hand, the precursor of IL-1β is not active and does not bind to the receptor. It requires a cleavage to become in the active form [44, 50, 51].

IL-1β is highly involved with autoimmune, infectious, degenerative and, especially, with autoinflammatory diseases. An important part of autoinflammatory diseases is caused by genetic defects in innate inflammatory pathways, and usually show their signals early in life. The first disease classified as autoinflammatory was tumor necrosis factor receptor associated periodic syndrome (TRAPS). Other examples are familial Mediterranean fever and adult and juvenile Still disease. This group of diseases promptly responds to the treatment with IL-1β blockade, with few exceptions. In many autoinflammatory diseases, there is a state of increased release of IL-1β. The precursor is converted to the active form through the action of Caspase-1. This enzyme is also found in the inactive form in tissue macrophages and dendritic cells, and requires conversion by autocatalysis to become active. However, it is in the active form in circulating human blood monocytes. The release of IL-1β from blood monocytes in highly controlled and takes several hours in healthy subjects. In patients with an autoinflammatory disease, more mature IL-1β is released when compared to healthy subjects, which leads to exacerbated inflammation. Despite of this group of diseases being characterized by severe inflammation, the amount of IL-1β released is not much greater than that released from healthy subjects. Currently, human anti-IL-1β monoclonal antibody is being developed to treat autoinflammatory diseases. Canakinumab was approved by Food and Drug Administration (FDA) in 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS). In 2016, Canakinumab was also approved for treating TRAPS, hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and familial Mediterranean fever (FMF) [50, 51].

IL-1Ra is a receptor antagonist. It is synthetized by the same cells that produce IL-1α and IL-1β (monocytes, macrophages, dendritic cells and others). The binding of IL-1Ra to the receptor does not involve conformational change and, hence, the co-receptor IL-1RAcP is not recruited. IL-1Ra regulates the activity of IL-1. However, to efficiently block the IL-1 response, it has to be in an amount approximately 100-folds greater than the agonists cytokines. Anakinra is a recombinant version of IL1-Ra used in the treatment of rheumatoid arthritis [44, 53].

IL-18 is synthetized as an inactive precursor, and, similarly to IL-1β, it needs cleavage by caspase-1 to become in the active form. The precursor form is present in almost all cells of the human body, likewise IL-1α. Usually diseases related to IL-18 appear when there is an imbalance between the amount of IL-18 and IL-18 binding protein, which is responsible for limiting the level of activity of IL-18. This cytokine is released usually from dying cells, once again like IL-1α [51, 54].

IL-18 was first described as "IFN-γ-inducing factor", because it was discovered as an inducer of IFN-γ production. However, alone, IL-18 does not induce the production of considerable amounts of IFN-γ. For that to happen, it has to act in association with IL-12. IL-18 promotes TH$_1$ and Th$_2$ cells responses, and also induces IL-13 production in T cells and NK cells together with IL-2. It also enhances NK toxicity by promoting the expression of Fas ligand in NK cells. IL-18 is involved in several autoimmune diseases, in myocardial infarction, metabolic syndromes and others [44, 55].

IL-33 is an alarmin cytokine, rapidly released upon cellular damage. It is involved mainly in type 2 immunity and inflammation. It acts in Th$_2$, in innate lymphoid cell-2 (ILC2), and in activated M2 polarized macrophages. This cytokine is expressed by keratinocytes, epithelial and endothelial cells, and monocytes. IL-33 is produced as a precursor, but, contrary to IL-1, caspase-1 transforms it in an inactive cytokine. The precursor is active and other proteases can cleavage it in more potent forms. IL-33 induces Th$_2$ response binding to ST2 and next recruiting IL-1RacP. The activity of IL-33 is controlled essentially by the binding to soluble ST2 and soluble IL-1RAcP. Levels of increased soluble ST2 are present in various inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis [44, 50, 56].

IL-36α, IL-36β and IL-36γ are receptor agonists, while IL-36Ra is a receptor antagonist that blocks the activation of the receptor and competes with IL-36, acting as a regulator. These cytokines are included in the interleukin-1 family because they share homology to the first members of the family. Their homology to IL-Ra and IL-1β varies from 20 to 52%. Furthermore, IL-36β and IL-36γ have the core 12-fold, β-trefoil structure and lack a signal peptide, particular features of IL-1 family. All these cytokines need an N-terminal processing to become in the active form, but the enzyme responsible for this process is still not known. IL-36 cytokines are predominantly found in skin cells, and that is why they are related with several skin disorders, such as psoriasis. After binding to the receptor (IL-36R and IL-1RAcP co-receptor), dendritic cells are activated and participate in the polarizing of T-helper responses [50, 52, 57].

Different from the other members of the family, IL-37 is an anti-inflammatory cytokine, and reduces innate inflammation as well as acquired immune responses. Its presence has already been reported in skin, tonsils, esophagus, placenta, breast, prostate and colon. There are five different isoforms of IL-37: IL-37a, IL-37b, IL-37c, IL-37d and IL-37e, expressed in different locations of the human body. So far, IL-37b, which contains a 12β-strand trefoil, typical of the IL-1 family, appears to be the most biologically active, and therefore the object of the majority of studies. IL-37 suppresses the production of pro-inflammatory cytokines, such as IL-1A, IL-6, CC chemokine ligand (CCL-12), colony-stimulating factors (CSF-1 and CSF-2), chemokine ligand-13 (CXCL-13), IL-1β, IL23-A and IL1RA, and also inhibits dendritic cell activation [58–60].

IL-38 is the most recent member of the Interleukin-1 family, identified in 2001. It binds to the same receptor that the IL-36 cytokines, IL-36R. However, it acts as an antagonist, similarly to IL-36Ra. Therefore, IL-38 acts reducing inflammatory response. IL-38 shares 41% homology with IL-1Ra and 43% with IL-36Ra. This cytokine is present in skin, tonsil, thymus, spleen, fetal liver and salivary glands. The properties and biological activities of IL-38 are still being studied [52, 61, 62].

4.2. Interleukin-2 family

The IL-2 cytokine family, also known as the common γ-chain family, is composed by ILs 2, 4, 7, 9, 15 and 21. All these ILs bind to the common γc receptor, also called CD132. These cytokines act as growth and proliferation factors for progenitors and mature cells [44, 63].

IL-2 is the first member of the common γ-chain family, previously known as T cell growth factor. This cytokine is mainly produced by CD4^{+} and CD8^{+} T cells, but can be also expressed by dendritic cells and NKs. The IL-2R is composed by three subunits (CD25, CD122 and common γc), all necessary to binding to IL-2. IL-2 acts in the development of regulatory T (Treg) cells, as a B cell growth factor, stimulates antibody synthesis and promotes proliferation and differentiation of NK cells and T helpers. IL-2 has been extensively used as an anti-cancer therapy [44, 63–65].

IL-4 is produced by Th$_2$ cells, basophils, eosinophils and mastocytes. It has two receptors: IL4-R type I, which binds only to IL-4 and is composed by CD124 (IL-4rα) and CD 132; and type II, which binds to IL-4 and to IL-13, and it consists in IL-4Rα and IL-13Rα1. These receptors are spread all over the human body. IL-4 is known to play several different roles, regulating allergic conditions and activating the immune response against extracellular parasites (B cell class switching to IgE). It is the main cytokine to stimulate development of Th$_2$ cells. Dupilimab is an IL-4 receptor antagonist approved in 2017 by FDA for treatment of eczema [44, 66, 67].

IL-7 is a homeostatic cytokine. It can be found essentially in T cells, progenitors of B cells and bone marrow macrophages. As the other members of the family, its receptor (IL-7R) consists in the common γ-chain fraction, along with another unit, the IL-7Rα (CD127). IL-7 is involved in the survival and proliferation of thymocytes and in the development of naïve and memory B and T cells, mature T cells and NKs. Deficiencies related to IL-7 result in immunodeficiency, autoimmune diseases and leukemia [44, 68].

IL-9 is mainly produced by Th$_2$ cells, but it is also expressed in less amounts by eosinophils and by mastocytes of asthmatic patients. Its receptor, IL-9R, is composed by the CD132 and IL-9Rα units. IL-9 is a potent growth factor for T cells and mastocytes, and some of it activities include the inhibition of cytokine production by Th$_1$ cells, IgE production, and mucus secretion by bronchial epithelium. Recently, a new subset of effector T cells was discovered, Th$_9$, and it is believed that it is intimately related with IL-9 production. IL-9 is associated to allergic diseases and protection from helminthic infections. This cytokine can be found in elevated amounts in Hodgkin lymphoma, hence, IL-9 antagonists are being studied as a potential treatment for this disease [44, 69, 70].

IL-15 is structurally homologous to IL-2. The receptor, IL-15R, is composed by the CD132 subunit common to the family, and also by IL-15Rα and IL-2Rβ chains. IL-15 is produced by keratinocytes, skeletal muscle cells, monocytes and activated CD4^{+} T cells, in response to signals that trigger innate immunity. IL-15 has some identical functions to IL-2, such as T cell activation and stimulation of NK cell proliferation, but it also involved with CD8^{+} memory cell, NK cell, and NKT-cell homeostasis. Increased levels of IL-15 were reported in autoimmune disorders, such as rheumatoid arthritis, psoriasis and celiac disease [44, 71].

IL-21 is produced by T cells, NKT cells and Th$_{17}$. The receptor, IL-21, is present in various parts of the human body and consists in CD132 and IL-21R. This cytokine is involved with B cells functions, and also increases the proliferation of CD8$^+$ T cells, NK cells and NKT. IL-21 is currently being studied as anti-cancer therapy [44, 64].

5. Other cytokines

In addition to the aforementioned cytokines, other also deserves attention, such as chemokines. The chemokines represent a large family of structurally homologous cytokines that stimulate leukocytes movement and regulate the migration of them from the blood to tissues, in a process named chemotaxis. They control homeostatic immune cells, such as neutrophils, B cells, and monocytes, trafficking between the bone marrow, blood and peripheral tissues. Therefore, they can be classified as chemotactic cytokines [33, 72].

There are about 50 human chemokines, classified into 4 families according to the location of N-terminal cysteine residues. The two major families are CC and CXC chemokines, in which the cysteine residues are adjacent on CC family, and are separated by one amino acid on CXC family. In general, members of CC chemokines are chemotactic for monocytes, and a small subset of lymphocytes, while CXC chemokines are more specific for neutrophils. The best-known chemokine is IL-8, or CXCL8, which belongs to the CXC chemokine family, and is responsible for neutrophil recruitment and for the maintenance of the inflammatory reaction. On the other hand, the monocyte chemoattractant protein-1 (MCP-1) or CCL2, and CCL11 or eotaxin, are examples of CC chemokines, which acts on recruitment of a variety of leukocytes, but especially monocytes, and eosinophils, respectively [33, 73, 74].

The chemokines receptors are expressed on all leukocytes and are divided in two groups: G protein-coupled receptors with seven-transmembrane α-helical segments, and atypical receptors, which appear to attenuate inflammation by scavenging chemokines, independently of G protein. Each receptor subtype is capable of binding to various chemokines of the same family, and a single chemokine can bind to more than one receptor. Despite of this factor, a lot of chemokines presents a great tissue and receptor specificity [72, 73].

Chemokines can be produced constitutively in various tissues, and are responsible for regulating the traffic of leucocytes, especially lymphocytes, through peripheral lymphoid tissues. However, the best-known activity of chemokines is the involvement on inflammatory reactions. Recruitment of macrophages, neutrophils and T cells to the site of inflammation is strongly stimulated by chemokines. In fact, they represent a secondary pro-inflammatory mediator that is induced by primary pro-inflammatory mediators, such as IL-1 or TNF. In general, members of the chemokines family induce recruitment of well-defined leukocyte subsets, differently of the classic leukocyte chemoattractants. They induce the movement of leukocytes, and consequently promote their migration to a specific local, by stimulating actin filaments [33, 72–74].

Beyond the involvement of the chemokines on acute inflammatory reactions, and the regulation of the traffic of leukocytes through peripheral lymphoid, independently of the presence of inflammation, some kind of chemokines can promote angiogenesis and wound healing,

associated mostly with CXC family, while other are involved in the development of diverse nonlymphoid organs [73, 74]. They also have an important role in the priming of naive T cells, in effector and memory cell differentiation, and in regulatory T cell function [72].

Besides chemokines, there are cytokines that stimulates hematopoiesis, such as the colony-stimulating factors (CSFs), which contributes to the growth of progenitors of monocytes, neutrophils, eosinophils and basophils, as well as activating macrophages. Immune and inflammatory reactions uses leukocytes, due to the recruitment induced by some kinds of cytokines, so new must be produced [73, 74]. Additionally, the GM-CSF (granulocyte-macrophage colony-stimulating factor) and M-CSF (macrophage colony-stimulating factor) have, like some other cytokines, a pro-inflammatory action, and exhibit a connexon between the expression of them and TNF, IL-1, IL-23 and IL-17 [75].

Finally, other cytokines can be highlighted: TGF-β, LIF, Eta-1 and oncostatin M. The TGF-β is responsible for the chemoattraction of monocytes and macrophages, but also it has an anti-inflammatory effect, by inhibiting the lymphocyte proliferation. LIF and oncostatin M induce the production of acute-phase protein, while Eta-1 stimulates the production of IL-2, and inhibits the production of IL-10 [73].

6. Cytokines and autoantibodies

On this topic, the association between the cytokines and autoimmune diseases will be reviewed, but emphasis will be given to these ones: systemic lupus erythematosus, type 1 diabetes mellitus, multiple sclerosis, vitiligo and heart failure.

The impossibility of differentiating between own and non-own (strange) could result in the synthesis of antibodies against the components of the organism (autoantibodies), which could be extremely deleterious [73]. The organism is characterized by a failure of the normal mechanism of self-tolerance, resulting in reactions against one's cells, in the absence of any present infection or another cause, known as autoimmunity, and the diseases caused by this phenomenon are referred as autoimmune diseases [33, 76].

The pathogenesis of autoimmune diseases involves mainly the genetic susceptibility, and previous infections. In relation to infections, it is observed a recruitment of leukocytes into the affected tissue, resulting in the activation of tissue antigen-presenting cells (APC). Consequently, these APCs express costimulators and secrete T cell-activating cytokines, contributing to the breakdown of T cell tolerance. Therefore, the infection promotes the activation of T cells that are not specific for the pathogen, in a process called bystander activation. Additionally, microbes may engage toll-like receptors (TRLs) on dendritic cells, resulting on production of lymphocyte-activating cytokines, leading to the autoantibody production. This process was demonstrated in mouse models, and its influence in human autoimmune diseases remains unclear [33].

The systemic lupus erythematosus (SLE) is an autoimmune disease, characterized by the involvement of immune complexes formed from autoantibodies and their specific antigens

that are responsible for the clinical manifestation, especially glomerulonephritis, arthritis and vasculitis. The peripheral blood lymphocytes of patient presents an excessive production and response to type 1 IFNs, but the involvement of this cytokines on the development of the diseases is still uncertain [33]. In these patients, for instance, serum IFN-α and IFN-α-induced gene expression are frequently observed, implying that the molecular pathogenesis of this condition is mediated by type I IFN. It has also been shown that IFN-γ serum levels are increased in SLE patients, and in mouse models, the receptor of this cytokine was necessary to the disease development. The massive amount of circulating IFN correlates to disease severity, which is likely to be triggered by excessive pDC activation. Recently, clinical trials evaluating anti-IFN-α monoclonal antibodies for SLE have been conducted, exhibiting promising results. Moreover, a trial evaluating a monoclonal antibody that binds IFN-γ was conducted, but no significant improvements in the efficacy outcome measures were observed. Additionally, a recent study demonstrated that keratinocytes may participate on the pathophysiological of the cutaneous manifestation of the SLE, by increasing cell apoptosis and producing pro-inflammatory cytokines, especially IL-23, IL-12, IL-6, IL-17, (Th17-related cytokines), IL-10 and TFG-β [16, 30, 77, 78].

In parallel, another autoimmune disease widely studied that involves cytokines, besides several other factors, is the type 1 diabetes mellitus. This disease is characterized by pancreatic β cells destruction, which it is due to hypersensitivity reactions mediated by CD4$^+$ TH 1 cells reactive with islet antigens, the effect of cytotoxic T lymphocyte on lysis of islet cells, and local production of cytokines, especially TNF, IL-1, IL-21 and IFN-α. In some cases, the islets show cellular necrosis and lymphocytic infiltration, consisted of both CD4$^+$ and CD8$^+$ cells. Remaining islet cells often express class II MHC molecules, an effect of local production of INF-γ by the T cells [33, 73, 79]. The onset of young age of this disease may be associated with upregulation of growth factors, especially GM-CSF and IL-7. Other mediators overexpressed are the pro-inflammatory cytokine IL-1β, the regulatory cytokine IL-10, IL-27, and some Th17 cytokines (IL-17, IL-21, IL-23). Additionally, patients that involve to ketoacidosis, a serious complication of the disease, have a tendency for higher IL-8 and IL-10 levels [80].

In the same way, it stands out the rheumatoid arthritis, a chronic and systemic autoimmune disease described as a progressive disability on joints, particularly of the fingers, shoulders, elbows, knees and ankles that can promote systemic consequences like cardiovascular, pulmonary and skeletal disorders. It is characterized by the production of autoantibodies, like rheumatoid factor, cytokines, chemokines, hyperplasic synovium, osteoclastogensis and angiogenesis. The pro-inflammatory cytokines IL-1α/β, IL-8, IL-6, TNF-α, INF-y and some CSFs are responsible for the pathogenesis of this disease, and are involved with the intracellular molecular signaling pathway that causes chronic inflammation on synovial membrane. These cytokines, especially TNF-α, activates the leukocytes endothelial cells and synovial fibroblasts, and stimulates the production of collagenases that are responsible for the destruction of the cartilage, ligaments and tendons of the joints. Therefore, monoclonal antibody drugs, such as anti-TNF are approved for treatment of this disease [33, 75, 76, 81].

It is also believed that bone destruction in rheumatoid arthritis is due to overexpression of the TNF family cytokine receptor activator of nuclear factor KB (RANK), an essential mediator

that promotes maturation and activation of osteoclasts [33, 76]. Therefore, the cytokines on rheumatoid arthritis promote the autoimmunity, the destruction of joint tissue and maintain the synovial inflammation [82].

The multiple sclerosis is a neurodegenerative autoimmune disease of high mortality in adults, characterized by a chronic inflammation in the central nervous system with secondary demyelination due to leukocyte and cytokines infiltration of brain tissue and spinal cord. Clinical manifestations are weakness, paralysis and ocular symptoms [33, 73]. A recent study proposed the role of Th1 lymphocytes in the pathogenesis of the brain inflammation, with several cytokines involvement. Th1 lymphocytes produces mainly IFNγ (type II IFN) that is responsible for the production of other pro-inflammatory cytokines, and chemoattractants, such as IL-2, IFNγ, CC chemokines, like CCL5, CCL11 and CCL27 and CXC chemokines, especially CXCL1 and CXCL10. On the other hand, lower levels of circulating type I IFN are observed. Therefore, unlike SLE, multiple sclerosis treatment involves the administration of IFN-β. Additionally, an upregulation of CCL27 was found in cerebrospinal fluid of multiple sclerosis patients, demonstrating the possibility of its involvement on activation and migration of autoreactive immune effectors in the brain, and consequently a potential contribution for the pathogenesis of this disease [83].

Vitiligo, is another autoimmune disease, characterized by the skin depigmentation, which is associated to the production of antibodies against the melanocytes, and it is more frequent in patients that have other autoimmune diseases, like Grave's disease [73]. A variety of cytokines are increased in vitiligo patients in relation to healthy people. A recent systematic review demonstrated an association between the expression of some kind of cytokines in vitiligo skin, especially INF-γ, TGF-β, IL-1β, IL-17, and the chemokines CXCL9, CXCL10 and CXCL12. IFN-γ and IL-1β are closely related to the pathogenesis of vitiligo, but serum TGF-β and IL-17 are more abundantly expressed in relation to the others [84].

Finally, another disease that has the participation of cytokines on its pathogenesis is the heart failure, a chronic disease characterized by a cardiac impairment due to hypertension, myocardial infarction, arrhythmias and other heart diseases. A recent evidence showed the involvement of the adaptive immune system in the development and progression of heart failure, which is related to high mortality in adults. T cells, particularly TH1, and TH17 and B1 lymphocyte, contribute to the pathologic chronic inflammation, and cell migration. The inflammatory component of this disease, which has a closely relation to the morbidity and mortality, are the cytokines, including TNF-α, TNF-β, IL-1, IL-6, IL-7, IL-10 and IFN-γ, chemokines and cardiac autoantibodies. Those factors are associated with cardiomyocyte death and tissue remodeling by fibrosis, contributing to the left ventricle dysfunction, and consequently to disease progression. In detail, initially the dendritic cells and other antigen-presenting cells can process specific proteins of the myocardial tissue and theirs contact with memory B cells promotes the release of auto-antibodies, and consequently activates pro-apoptotic pathways, by antigen-dependent cell cytotoxicity, and complement-mediated cell cytotoxicity in health myocytes. Another characteristic of the pathogenesis of heart disease is the production of inflammatory mediators by B cells, such pro-inflammatory cytokines (TNF-α and IL-6) and chemokines,

which recruit monocytes involved with inflammation and heart remodeling, beyond the activation of T lymphocytes, leading to the production of other specific inflammatory cytokines (IFN-y and IL-2) [73, 85].

Selective immunosuppression of B-lymphocytes may be a promising therapeutic on acute and chronic heart failure, as the blockage of the immune mediators, such cytokines, once they are involved to the propagation of the disease [85].

In sum, different kinds of cytokines are involved on autoimmune diseases, which plays an important role especially on inflammatory process, and contributing to the pathogenesis, in most cases. Studies have been performed, in order to establish the association between cytokines and the evaluation of these diseases, with the objective of developing therapeutic strategies, such as anti-TNF for rheumatoid arthritis.

7. Conclusion

In this chapter, the main aspects regarding the different types of cytokines and their main functions were reviewed. Hence, the comprehensive and fundamental role of cytokines in the immune system could be thoroughly investigated. Additionally, the contribution of these molecules to the development of diseases, particularly related to autoimmunity, as well as its use as treatment approach for some clinical conditions was explored.

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