Alergologia Polska – Polish Journal of Allergology 2023; 10, 3: 210–219
DOI: https://doi.org/10.5114/pja.2023.131708
Received: 9.03.2023, Accepted: 12.07.2023.

Alergologia POLSKA
Polish Journal of Allergology

REVIEW PAPER/*PRACA POGLĄDOWA*

The role of cytokines and chemokines in the inflammatory response

Rola cytokin i chemokin w odpowiedzi zapalnej

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ABSTRACT

All organisms are interconnected through the processes and relationships that take place within them. It is the interdependence of organs that forms the overall complex. In the course of evolution, the immune system in some species has been refined. However, in the event of allergy or foreign body penetration, serious damage can occur. The immune system is a barrier that provides organisms with protection from both external and internal influences. The body's immune response is one of the most basic and important functions of the human body. When seemingly harmless antigens of a chemical or biological nature enter the body, the immune system activates antibodies to prevent the antigen from multiplying in the body. As part of inflammation, the immune system is mobilized, with immune cells detecting the degree and severity of damage to blood vessels and the lymphatic system. Subsequently, the allergen is cleared or prevented from spreading through the response of immunocompetent cells.

KEY WORDS

immune system, inflammation, cytokines, chemokines, immunotherapy.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Inflammatory and immune responses play an important role in the immune system. Exposure to substances (allergens) can cause damage to internal or external structures, e.g. tissue damage, or subsequently induce an adequate immune response [1–4]. The first and fundamental step of the immune system is to recognize the danger and subsequently react to what threatens the organism. The immune system recognizes anything that causes stress or can cause tissue damage as a threat. Exogenous molecules (pathogenic molecular patterns – PAMPs) can activate immune cells. In addition to exogenous molecules, endogenous alarmins (produced in stressful situations)

can also activate immune cells. According to Castellheim *et al*., damage-associated molecular patterns (DAMPs) can be categorized as exogenous and endogenous molecular patterns. The innate immune system is the first to respond, followed by lymphocyte activation and production of pro-inflammatory cytokines. The inflammatory response contributes to further tissue damage. The main prerequisite for the development of inflammation is the activation of immune system cells. Subsequently, pattern-recognition receptors (PRRs) trigger the production of inflammatory mediators that can alter tissue or organ function [3–5].

IMMUNE SYSTEM, INNATE AND ADAPTIVE IMMUNITY

The immune system is a collection of cells, chemicals and processes that protect the human body from foreign antigens such as microbes, cancer cells, viruses and others. The immune system fights against various pathogens of biological, chemical or physical nature that may be present in the blood, tissues or skin [4, 6]. The regulation of the immune response is mediated by antigen presenting cells (APCs) – monocytes, dendritic cells, phagocytic cells, which are incorporated under innate immunity, and T helper (Th) lymphocyte subclasses Th1, Th2, which are a part of adaptive immunity [7, 8].

Innate immunity is a rapid immune response that takes place within minutes (or hours) of being attacked by an agent. It is the first and general mechanism against a pathogen [4, 5, 9]. Since it has no immunological memory, it is unable to recognize (or remember) a pathogen that has also infected the body in the past. It can be argued that innate immunity consists of four protective barriers: anatomical (skin, mucosa), physiological (pH, temperature, chemical mediators), endocytic and phagocytic, inflammatory barrier, and cells that release cytokines and inflammatory mediators (e.g., macrophages, mast cells, natural killer cells). Innate immunity includes pattern recognition receptors (PRRs). Through these receptors, a certain number of immune cells can find and rapidly respond to a wide range of pathogens that have molecular patterns associated with the pathogen (common structures – bacterial wall components, lipopolysaccharides, RNA produced during viral infection etc.) – molecular patterns associated with pathogens – PAMPs [9, 10]. Innate recognition initiates basic cellular responses to host cell interaction with invading microbes. PAMP innate recognition activates innate immune responses to generate immunogenic signals. These in turn induce some specific components of adaptive immunity [11].

Adaptive (staggered) immunity is antigen-dependent and involves a time lag between antigen exposure and the maximal response. The hallmark of adaptive immunity is its memory capacity in generating a faster and more effective immune response [9, 12]. The cells of the adaptive immune system are T-lymphocytes and B-lymphocytes, which are highly motile. After development in primary lymphoid organs (thymus, bone marrow), they move to secondary lymphoid organs including the spleen and lymph nodes. In these organs, they serve to capture antigens circulating in the blood and lymph. Adaptive immune responses may also respond to indirect stimuli from mucosal antigen-presenting cells (APCs) that migrate to secondary organs. Lymphocytes can then travel to many sites in the body where they perform effector functions [13, 14].

INFLAMMATION

The body's response to injury, chemical toxins, invading microorganisms or hypersensitivity characterised by increased blood flow or permeability of blood vessels, leukocytes and inflammatory mediators (cytokines) is called inflammation. Infection causing inflammation in the body may be bacterial, viral, fungal or parasitic in nature. Currently, inflammation is present in many diseases, but in recent decades, inflammation that is at the cellular or molecular level has become more prevalent. The number of individual diseases that are closely associated with molecular markers of inflammation continues to increase. An anti-inflammatory therapy that is effective in a given disease may be equally effective in another, opening up the possibility for intervention [15]. The chronic phase involves the development of humoral cellular responses to factors present at the site of damage [16, 17]. The immediate activation of the innate immune system depends on the detection of conserved microbial motifs (PAMPs), in which macrophages and mast cells are involved [18]. Once their presence is detected, innate immunity triggers defence mechanisms that lead to the development of inflammation and host resistance to infection. These include the release of antimicrobial agents, phagocyte clumping, peptide release, and the production of cytokine, chemokine, and prostanoid groups [19, 20]. Inflammation is defined as a complicated process consisting of several steps, the main function of which is to prevent the multiplication of pathogens in order to destroy or eliminate them. It is caused by the coordinated secretion of substances, mainly from leukocytes (white blood cells), which cause redness, swelling or pain, dilatation of blood vessels, and serve as a marker of the site of infection for other leukocytes. Once the leukocytes are activated, a subset of PRRs activate the protease caspase-1, which causes the maturation of cytokines IL1β and IL18. Cell adhesion molecules and chemokines facilitate ex-

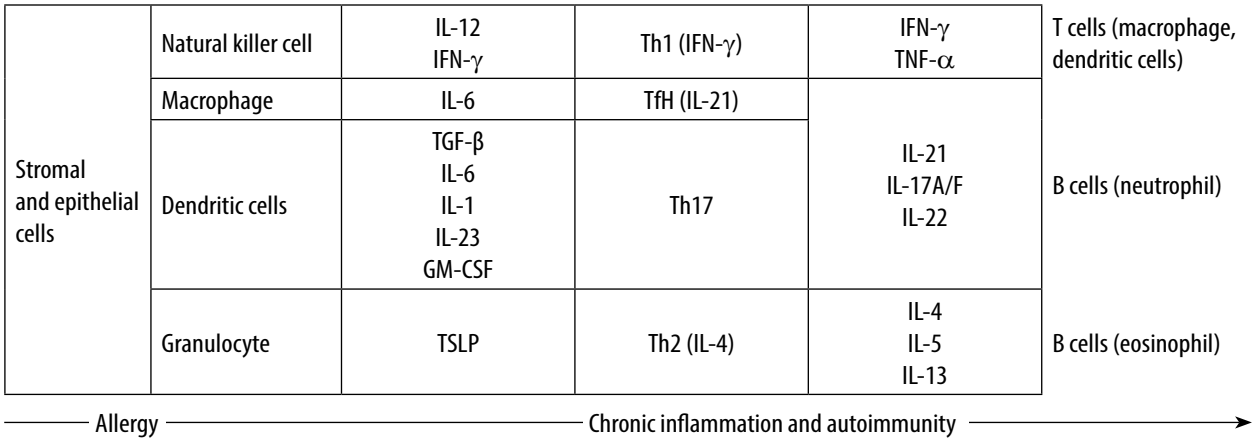

FIGURE 1. Inflammation and cytokine function in the immune system

travasation of leukocytes from the circulation to the affected site; receptors (G-protein coupled) are stimulated by chemokines. Binding-activated signals regulate effector functions and leukocyte motility [21]. Inflammation leads to an increase in temperature at the site of infection, which is detrimental to the spread of pathogens. Depending on the site of action, it can be local or systemic (total) [22] (Figure 1).

Production of pro-inflammatory cytokines that promote activation of CD4+T- cells and their subsequent differentiation into T-helper subsets.

CYTOKINES AS KEY MODULATORS

These small proteins represent a key modulator of inflammation and are important for tissue immunity. They have a low molecular weight and act as messengers that alter the behaviour of their own or another cell [23]. Through a network of interactions, they are involved in acute and chronic inflammation. Cytokine receptors are localized on the surface of human cells. Those that are soluble can be found in small amounts in the plasma. They are also referred to as cells regulating cytokine function, thereby influencing the nature of disease states [24–26]. Through binding to specific receptors, cytokines transmit intracellular signals. Mostly, they influence cell activation, division, apoptosis or movement. Their action is endocrine, autocrine or paracrine. Interleukins are products of leukocytes acting on other white blood cells. Interferons have a defensive role; colony-stimulating factors serve for differentiation and proliferation of stem cells [27, 28]. Cytokines are divided into several classes based on their structure, function, or source, but a particular cytokine may also belong to multiple classes within a single structure or origin.

Currently, 18 types of cytokines are classified under the name interleukin (IL). Other cytokines are retained under their original name, e.g. tumour necrosis factor (TNF). Cytokines play an important role in inflammation and the subsequent immune response. Species that promote inflammation are referred to as pro-inflammatory, while others suppress the activity of pro-inflammatory cytokines and are referred to as anti-inflammatory cytokines [29, 30].

Different cytokines can have positive and negative effects on cell function, playing a role not only in the immune response and inflammation, but also in reproduction, trauma, and disease formation (cancer, asthma, heart and endocrine diseases, and others). The nature of the immune response depends on the nature of the cytokines that are produced, but often a synergy of multiple cytokines is required to manifest a response. Depending on the cellular source or immune response, individual cytokines may have different functions. Nuclear factor kappa B (NF-κB) is a major mediator of inflammatory action [30–33]. Depending on the nature of inflammation, cytokines can be divided into acute inflammation-inducing cytokines (IL-1, TNF-α, IL-6, IL-11, IL-8, chemokines, G-CSF, and others) and chronic inflammation-inducing cytokines (humoral – IL-4, IL-5, IL-6, IL-7, IL-13, and cellular – IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, and others) [17]. The pro-inflammatory cytokines IL-1 and TNF have multiple pro-inflammatory properties that contribute to the disease. In studies where a cytokine injection has been given to animals or humans, most of the known findings to date have been elucidated. Due to the establishment of a specific blockade of either IL-1 or TNF, or both, a reduction in the severity of inflammation has been noted. These forms are considered to be the primary cytokines involved in inflammation [34]. Specifically, the type 2 cytokines interleukin-4 (IL-4), IL-5 and IL-13 are associated with asthma, which is defined as a chronic inflammatory disease. These cytokines increase mucus

production, airway eosinophilia and bronchial hyperresponsiveness [35].

INTERLEUKIN-1

This interleukin represents a major endogenous pyrogen that is significantly involved in the pathogenesis of many diseases. Because of its important role in inflammatory responses and on the basis of cDNA clones, IL-1 has been subdivided and concretized into IL-1α and IL-1β. These two pro-inflammatory cytokines have been intensively studied in the field of immunology precisely because of the inflammatory response [36]. It is produced in epithelial and mucosal cells, organs (kidney, lung, liver and heart). IL-1β is constitutive only in resident macrophages with low expression. When tissue damage occurs, IL-1α is released by necrotic cells. It acts as a warning signal to leukocytes and initiates sterile inflammatory responses that subsequently activate their own IL-1α production. In this way, a loop of self-inflammation is established, resulting in tissue damage [37, 38]. IL-1β represents an inflammatory mediator that promotes the attraction of granulocytes to the site of inflammation and induces the expression of prostaglandins during the acute inflammatory response. It is linked to adaptive and innate immunity via T cells. It also ensures the production of cytokines by Th17 cells, resulting in the development of chronic diseases. IL-1β has an important defensive function, particularly against infections caused by microorganisms such as *Candida, Salmonella, Listeria* and *Mycobacterium tuberculosis* [39–41].

INTERLEUKIN-2

It is one of the first characterized cytokines of the lymphocyte hormone family. It is essential for the generation and regulation of the immune response, maintenance of homeostasis and is an important expansion factor for most T cells. It is predominantly produced by activated CD4+ and CD8+ T-lymphocytes [42, 43]. Its function is to stimulate NK (natural killer) cells and induce cytolytic activity. At high levels, it stimulates B cells to divide and subsequently produce antibodies. Through suppression of Th17 differentiation and increase in cell death, it is a crucial factor for the induction and resolution of inflammatory processes [44].

INTERLEUKIN-3

IL-3 is one of the basic representatives of glycoproteins with a characteristic three-dimensional structure. It is a hemopoietic factor with the ability to stimulate the production and activity of various types of blood cells. This cytokine usually acts at the site of inflammation, close to the cellular source, since it mainly targets cells belonging to the lymph haemopoietic system [45]. The interface between the blood component and the tissues is the vascular endothelium, which is involved not only in the regulation of haematopoiesis but also in inflammatory responses. Its central role is to control the infiltration of leukocytes to the site of inflammation and to promote their adhesion and transmigration. Endothelial cells are the source of granulocyte colony-stimulating factors (G-CSF) and granulocyte and macrophage colony-stimulating factors (GM-CSF). These in turn stimulate the production and function of granulocytes, monocytes and IL-6, which represent an important role in the acute phase of inflammation [46–48].

INTERLEUKIN-4

IL-4 is defined as a complex glycoprotein that is produced by mast cells, basophils, eosinophils, neutrophils and Th cells. This interleukin increases the expression of the major histocompatibility complex (MHC) and promotes the secretion of IgE and IgG1. It also inhibits the secretion of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6). It upregulates CD13 on the cell surface, thereby inactivating inflammatory peptides [49, 50]. IL-4 elicits many responses that are closely linked to allergy and asthma through the regulation of Th2, which down-regulates IL-4, IL-5, IL-9, and IL-13, which are involved in the allergic response [51].

INTERLEUKIN-5

This dimeric cytokine controls differentiation from B-cells to antibody-secreting cells, and also plays an important role in the growth and differentiation of eosinophils [52]. Although it is not involved in IgE production, it acts on mast cells, resulting in the release of histamine, which acts in allergies. In the pharmaceutical industry, IL-5 is an investigational subject, mainly due to its less pleiotropic nature, which could make a drug targeting this cytokine significantly alleviate asthma attacks without compromising the patient's health [53].

INTERLEUKIN-6

It belongs to a group of pleiotropic cytokines with a wide range of functions. It is produced by lymphoid and non-lymphoid cells. Its functions include regulation of oncogenesis, inflammation, immune response, acute response and haematopoiesis, induction of B-cell differentiation, and enhancement of IL-3-induced multipotential colony formation of hematopoietic stem cells [54, 55].

However, excessive IL-6 production may be one of the consequences of the development of many diseases – psoriasis, myeloma, Castleman's disease, rheumatoid arthritis, and others [56].

INTERLEUKIN-7

It represents a stromal cell product, providing critical signals to lymphoid cells. It also promotes the growth of progenitor B-cells, regulates the development of immune system cell homeostasis (T-cells, B-cells and NK cells). Its important role is maintenance of health and prevention against diseases, since immunodeficiency occurs in congenital IL-7 deficiency [57]. Due to the positive results of IL-7 effects, it is likely to be an effective immunotherapy in various acute and chronic diseases. In the treatment of sepsis, through immunoadjuvant therapy, IL-7 has been shown to restore lymphocytes after septic shock [58]. Therapy has also shown its positive effects in coronavirus disease, which has posed a huge challenge to the field of medicine and science [59].

CHEMOKINES

Chemokines are small proteins that belong to the cytokine family. They are structurally related to cytokines, but contain four cysteines at certain positions. Their role is to control the migration of cells to sites of tissue damage or infection by binding appropriate receptors, thereby modulating the movement and function of target cells, especially leukocytes [60, 61]. In addition to the central role of chemotactic migration, they can also stimulate targeted and nontargeted migratory behaviours (chemokinesis, hypoxia, haptokinesis) [62]. The key role of chemokines lies in inflammation and the body's immune response. Chemokines are essential mediators of cancer-related inflammation and are present in the tumour area in chronic inflammation [63]. The role of inflammatory chemokines is to activate leukocytes to initiate wound healing through the immune response. Homeostatic and maintenance chemokines are involved in adaptive immune responses. Homeostatic chemokines are expressed in specific tissues, whereas the production of inflammatory chemokines can be mediated by many cell types at multiple sites [33].

INTERLEUKIN-8

During the inflammatory process, this tumorigenic, angiogenic, and chemotactic cytokine attracts basophils, neutrophils, and T cells to the site of inflammation or tissue damage, defining it as an inflammatory mediator. It is involved in neutrophil activation, with its secretion being increased by multiple cell types (monocytes, macrophages, neutrophils, bone marrow cells, etc.) in response to an inflammatory response [64].

INTERLEUKIN-9

Interleukin-9 is a multifunctional cytokine that is produced by CD4+ cells, specifically Th2, and also plays an important role as a T-cell growth factor. It ensures the proliferation and differentiation of mast cells and hematopoietic progenitor cells. IL-9 promotes the secretion of IgE receptors by mast cells, thereby promoting the growth of eosinophils. This implies that it has an important role in the development of allergic reactions, as confirmed by the increased expression of IL-9 in lymphocytes from the bronchoalveolar lavage fluid in asthmatic patients [65]. During an allergic reaction it is responsible for the negative course, but is highly effective during parasitic infection when it helps to eliminate the pathogen [66, 67].

INTERLEUKIN-10

An important role of IL-10 is to promote immune tolerance. This immunosuppressive cytokine is produced by Th2 monocytes and other cells of innate and adaptive immunity. Through the reduction of Th1 cytokines, it can prevent antigen presentation in macrophages, while suppressing cytokine secretion, thus representing an important role in allergies [68, 69]. It plays a key role in the prevention of inflammatory and autoimmune diseases. Insufficient expression of IL-10 may lead to an increased risk of inflammatory response which may lead to tissue damage or impaired immunopathology. However, certain pathogens have the ability to use immunosuppression of IL-10 to limit the body's immune response, which in turn leads to persistent inflammation. Therefore, identification of the cellular sources and mechanisms of IL-10 is critical for the development of therapeutic implications that will lead to overcoming pathological disorders [70–72].

INTERLEUKIN-11

This cytokine is expressed in the central nervous system and gastrointestinal tract. It has hematopoietic effects on thrombopoietic activity [73]. It stimulates proliferation of megakaryocyte progenitor cells and induces their maturation, resulting in increased platelet expression. It produces fibroblasts, epithelial cells and various stromal cells. It is required for inhibition of adipocytes, activation of osteoclasts, stimulation of tissue fibrosis, regulation of chondrocyte and B-cell fibrosis. IL-11 plays a key role not only in haematopoiesis, but also in bone metabolism, tissue remodelling, and, due to its effects, it has a protective function in mucosal tissues [74].

INTERLEUKIN-12

IL-12 is produced by transformed B-cells and is defined as a heterodimeric protein. Its properties link innate and adaptive immunity, and through induction of Th1 differentiation it can act as a key regulator of the immune response. It induces cell-mediated immunity through T cells and also has immunomodulatory and antiangiogenic effects which subsequently lead to the use of IL-12, in combination with other cytokines, as an antitumor agent whose future use represents a therapeutic agent in cancer patients [75].

INTERLEUKIN-13

The role of this cytokine is immunoregulation of B-cell and monocyte lineages, inhibiting the production of inflammatory cytokines. It plays an important role in allergy or asthma, where it causes the Ig isotype in B lymphocytes to change to IgE [76]. Despite sharing common signalling components with IL-4, IL-13 has distinct functions, particularly with respect to the phenotype of asthma, helminth infections or tumour growth. Through the release of excessive mucus and the promotion of bronchial hyperreactivity, IL-13 is an important component in the development of allergic inflammation. It is hypothesized that inhibition of IL-13 could be an important milestone in the treatment of asthma or allergic diseases [77, 78].

INTERLEUKIN-14

It represents a high molecular weight B-cell growth factor. Although its function is not fully elucidated, it is involved in the pathogenesis of autoimmune diseases e.g. Gravers' disease, Hashimoto's thyroiditis, sepsis etc. [79].

INTERLEUKIN-15

The function of pro-inflammatory cytokine IL-15 lies in the immune system through controlled inflammation. It is produced by multiple tissues or cell types: placenta, kidney, lung, skeletal muscle, cardiac tissue, fibroblasts, epithelial cells, monocytes, nerve cells, dendritic cells, macrophages. It provides initiation of proliferation and immunoglobulin production, stimulates proliferation of NK cells and activated CD4+ and CD8+ T cells. It is also able to differentiate malignant cells from normal B-lymphocytes, which proliferate in response to IL-15 as opposed to normal B-lymphocytes [80, 81].

INTERLEUKIN-16

Because of its ability to recruit CD4 T cells, it has been referred to as a lymphocyte chemoattractant. It is secreted by CD4 T cells, eosinophils and mast cells. It serves as a pro-inflammatory factor that is chemotactic for immune cells. It is of great importance in allergic reactions, where it is found in increased amounts in nasal tissues or bronchoalveolar lavage fluid of asthmatic patients [78, 82].

INTERLEUKIN-17

This cytokine represents a subset of Th17. Its role is protection against extracellular pathogens and stimulation of the inflammatory response in autoimmune diseases [83]. It is expressed by activated CD4+ and CD8+ T-lymphocytes. It is defined as a pro-inflammatory cytokine due to induction of the expression of mediators of inflammation. Elevated levels of IL-17 have been reported in several diseases including airway inflammation, arthritis, abscesses, cancer, psoriasis, and multiple sclerosis [84].

INTERLEUKIN-18

IL-18 is classified as an essential regulator of innate and acquired immune responses. It is expressed at sites of chronic inflammation, in cancer, autoimmune diseases and also in association with many infectious diseases [85]. This pro-inflammatory cytokine has multiple effects including the ability to promote Th1 development, inhibition of the production of anti-inflammatory cytokine IL-10, and induction of the expression of pro-inflammatory cytokines and chemokines. Its role is not only in the immune system, but also interferes with the nervous system, endocrine system or bone metabolism [86].

TUMOUR NECROSIS FACTOR

It has been described as a central cytokine in inflammatory responses, where it induces the expression of inflammatory genes, induces cell death and stimulates inflammatory immune responses [87]. The tumour necrosis factor is divided into two subunits, each with characteristic functions. TNF-α acts as a pathological component of autoimmune diseases. However, excessive activation of TNF-α results in chronic inflammation, which can lead to complications with a pathological character. Considering the mechanism, TNF-α is used to treat immune diseases in the form of various inhibitors [88]. This pro-inflammatory cytokine is produced by macrophages, monocytes, T cells, smooth muscle cells, fibroblasts or adipocytes [89]. One of the necessary steps for the development of inflammation is the interaction of cytokines, thus amplifying the reactions that these cytokines induce. TNF-α is usually released with interleukins, the most common of which is IL-1. When these cytokines work together, they modulate proinflammatory signals, increase chemok-

ine expression, and initiate the first-line response of the body's immune system [90]. TNF-β (lymphotoxin-α) is produced by T-lymphocytes and leukocytes, fibroblasts, astrocytes, and endothelial cells. It is involved in autoimmune disorders, lymph node development, and mediates the inflammatory process of the immune system [91]. It is essential for maintaining homeostasis; if TNF-β activity is reduced, autoimmune diseases occur [92].

GRANULOCYTE MACROPHAGE-COLONY STIMULATING FACTOR

This master regulator controls granulocyte and macrophage functions at all stages of maturation. This factor plays its role locally, at the site of inflammation. Inflammation mediated by this pro-inflammatory cytokine is involved in several types of autoimmune diseases (multiple sclerosis, rheumatoid arthritis). Therapeutic implications include the use of agents that block GM-CSF or its receptor. However, the effects of an inflammatory nature depend on the amount and presence of other cytokines [93] (Table 1).

CANCER IMMUNOTHERAPY

According to the WHO (2022), cancer caused nearly 10 million deaths worldwide in 2020 [94]. So far, the recommended treatment is surgery or chemotherapy. These methods are effective in terms of removing the tumour itself. However, they are not very effective in preventing metastatic spread through tumour cells. In the context of cancer immunotherapy, elimination of disseminated tumour cells and micrometastases represents a great potential [95, 96]. Several strategies are known in the use

TABLE 1. Signalling molecules involved in acute and chronic inflammation, their source and basic function

Signalling molecules	Source of expression	Main function
IL-1	Macrophages, epithelial cells	Proinflammatory alarmin cytokine, macrophage and Th17 cell activation
IL-2	T cells	T cell proliferation
IL-3	T cells	Bone marrow growth
IL-4	T cells	B cell activation, growth factor
IL-5	T cells	B cell growth factor
IL-6	Macrophages, T cells	Pyrogenic function, increased antibody production, induction of acute-phase reactants
IL-7	Lymphocytes	Stimulation of proliferation of immature cells
IL-8	Macrophages, T cells	Stimulation of the activity of neutrophils, inhibitor of leukocyte adhesion
IL-9	Th9 cells	Protection against helminth infections, activation of mast cells
IL-10	T cells	Inhibition of Th1 cells and cytokine release
IL-11	Bone marrow	Stimulates proliferation of megakaryocyte progenitor cells and induces their maturation
IL-12	Macrophages	Activation of the Th1 pathway, induction of interferon-γ from Th1 cells, CTLs and NK cells
IL-13	T cells, mast cells, basophils, eosinophils	Suppression of cytotoxic activity
IL-14	T cells, B cell tumours	Pathogenesis of autoimmune disorders
IL-15	Mononuclear phagocytes	Stimulation of NK and T cells growth
IL-16	CD4 T cells, eosinophils, mast cells	CD4 T-cell recruitment
IL-17	Th17 cells, NK cells, innate lymphoid cells	Promoting neutrophil inflammation, protection against bacterial and fungal infections
IL-18	Monocytes, dendric cells	Activation of the Th1 pathway, which acts in synergy with interleukin-12
TNF	Macrophages, NK cells, T cells, mast cells	Increasing the permeability of blood vessels
GM-CSF	Macrophages, T cells	Increase in neutrophils and eosinophils

of immune cells: monoclonal antibodies against tumour antigens, immune checkpoint inhibitors, vaccination, adoptive cell therapy (e.g., CAR-T cells), and cytokine administration. The chemokine system represents a potential treatment target in immunotherapy. Through their altered expression in malignant cells, leukocyte activation, tumour cell proliferation and metastases are enhanced in all stages of cancer [97, 98]. The role of cytokines in immunotherapy is to directly stimulate effector and stromal cells at the tumour site. It is known from various studies that cytokines have a rich antitumor response [99, 100]. Combination approaches have brought clinical success to many and have also improved the overall response rate of patients [101–103]. The current approach to cancer treatment through immunotherapy suggests that IL-7 has great potential to treat cancer by increasing the number of circulating CD4+ and CD8+ T cells [104].

CONCLUSIONS

Inflammatory immune responses are conditioned by a variety of mediators. In this study, we specifically focused on the key modulators, inflammatory and anti-inflammatory cytokines and chemokines, which have important roles in acute and chronic inflammation. A deeper exploration of this issue is essential not only in understanding the response of the immune system, but also in mediating immunotherapy in cancer treatment.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic (APVV-15-0556) and Grant agency of University of Prešov in Prešov (GaPU 12/2023).

REFERENCES

1. McCombe PA, Read SJ. Immune and inflammatory responses to stroke: good or bad? Int J Stroke 2008; 3: 254-65.
2. Schindler LW. Understanding the Immune System 1991; 40. ISBN 0-7881-1519-7.
3. Pharm P. The Immune System. Fourth International Student Edition. Norton & Company 2014; 509.
4. Hrubiško M. a kol. Alergológia. Martin: Osveta a spol. s.r.o. 2003. ISBN 80-8063-110-7.
5. Castellheim A, Brekke OL, Espevik T, et al. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol 2009; 69: 479-91.
6. Kobayashi K, Inohara N, Hernandez LD, et al. RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. Nature 2002; 416: 194-9.
7. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci 2002; 966: 290-303.
8. Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metabol 1999; 10: 359-68.
9. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2018; 14: 49.
10. Aristizábal B, González Á. Innate immune system. In: Autoimmunity: From Bench to Bedside. Anaya JM, Shoenfeld Y, Villarraga AR, et al. (ed.). El Rosario University Press, Bogota 2013.
11. Kubelkova K, Macela A. Innate immune recognition: an issue more complex than expected. Front Cell Infect Microbiol 2019; 9: 241.
12. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immunol 2010; 125: S33-40.
13. Hedrick SM. Thymus lineage commitment: a single switch. Immunity 2008; 28: 297-9.
14. Schmid-Schönbein GW. Analysis of inflammation. Annu Rev Biomed Eng 2006; 8: 93-151.
15. Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. Front Biosci 1997; 2: 12-26.
16. Aldrich MB, Sevick-Muraca EM. Cytokines are systemic effectors of lymphatic function in acute inflammation. Cytokine 2013; 64: 362-9.
17. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454: 428-35.
18. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124: 783-801.
19. Fritz JH, Ferrero RL, Philpott DJ, Girardin SE. Nod-like proteins in immunity, inflammation and disease. Nat Immunol 2006; 7: 1250-7.
20. Newton K, Dixit VM. Signaling in innate immunity and inflammation. Cold Spring Harb Perspect Biol 2012; 4: a006049.
21. Evin L. Poruchy imunitného systému. Národný portál zdravia 2022.
22. Parkin J, Cohen B. An overview of the immune system. Lance 2001; 357: 1777-89.
23. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease. Biochim Biophys Acta 2014; 1843: 2563-82.
24. Castellheim A, Brekke OL, Espevik T, et al. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol 2009; 69: 479-91.
25. Heaney ML, Golde DW. Soluble receptors in human disease. J Leukoc Biol 1998; 64: 135-46.
26. Nicholas C, Lesinski GB. Immunomodulatory cytokines as therapeutic agents for melanoma. Immunotherapy 2011; 3: 673-90.
27. Hewison M. Vitamin D and innate and adaptive immunity. Vitamins Hormones 2011; 86: 23-62.
28. Dinarello CA. Proinflammatory cytokines. Chest 2000; 118: 503-8.
29. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci 2002; 966: 290-303.
30. Bartekova M, Radosinska J, Jelemensky M, Dhalla NS. Role of cytokines and inflammation in heart function during health and disease. Heart Fail Rev 2018; 23: 733-58.
31. Cannon JG. Inflammatory cytokines in nonpathological states. Physiology 2000; 15: 298-303.
32. Saini HK, Xu YJ, Zhang M, et al. Role of tumour necrosis factor-alpha and other cytokines in ischemia-reperfusion-induced injury in the heart. Exp Clin Cardiol 2005; 10: 213-22.
33. Borish LC, Steinke JW. 2. Cytokines and chemokines. J Allergy Clin Immunol 2003; 111: S460-75.

34. Dinarello CA. Role of pro-and anti-inflammatory cytokines during inflammation: experimental and clinical findings. J Biol Regul Homeost Agents 1997; 11: 91-103.
35. Lambrecht BN, Hammad H, Fahy JV. The cytokines of asthma. Immunity 2019; 50: 975-91.
36. March CJ, Mosley B, Larsen A, et al. Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. Nature 1985; 315: 641-7.
37. Gresnigt MS, van de Veerdonk FL. Modulating inflammatory cytokines: IL-1. Immune Rebalancing 2016; 151-71.
38. Chen CJ, Kono H, Golenbock D, et al. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. Nat Med 2007; 13: 851-6.
39. Ben-Sasson SZ, Hu-Li J, Quiel J, et al. IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci 2009; 106: 7119-24.
40. Kullberg BJ, Van't Wout JW, van Furth RA. Role of granulocytes in increased host resistance to Candida albicans induced by recombinant interleukin-1. Infect Immun 1990; 58: 3319-24.
41. Özören N, Masumoto J, Franchi L, et al. Distinct roles of TLR2 and the adaptor ASC in IL-1β/IL-18 secretion in response to Listeria monocytogenes. J Immunol 2006; 176: 4337-42.
42. Malek TR. The biology of interleukin-2. Annu Rev Immunol 2008; 26: 453-79.
43. Smith KA. Interleukin-2: inception, impact, and implications. Science 1998; 240: 1169-76.
44. Hoyer KK, Dooms H, Barron L, Abbas AK. Interleukin-2 in the development and control of inflammatory disease. Immunol Rev 2008; 226: 19-28.
45. Schrader JW. Interleukin-3. Growth Factors Cytokines Health Dis 1997; 2: 49-84.
46. Korpelainen EI, Gamble JR, Vadas MA, Lopez AF. IL-3 receptor expression, regulation and function in cells of the vasculature. Immunol Cell Biol 1996; 74: 1-7.
47. Seelentag WK, Mermod JJ, Montesano R, Vassalli P. Additive effects of interleukin 1 and tumour necrosis factor-alpha on the accumulation of the three granulocyte and macrophage colony-stimulating factor mRNAs in human endothelial cells. EMBO J 1987; 6: 2261-5.
48. Jirik FR, Podor TJ, Hirano TO, et al. Bacterial lipopolysaccharide and inflammatory mediators augment IL-6 secretion by human endothelial cells. J Immunol 1989; 142:144-7.
49. Curtis JL. Interleukins| IL-4. Encyclopedia of Respiratory Medicine 2006; 354-9.
50. Smiley ST, Grusby MJ. Interleukin 4. Encyclopedia of Immunology 1998; 1451-3.
51. Kelly-Welch A, Hanson EM, Keegan AD. Interleukin-4 (IL-4) pathway. Sci STKE 2005; 2005: cm9.
52. Takatsu K. Interleukin-5. Curr Opin Immunol 1992; 4: 299-306.
53. Mak TW, Saunders ME. Cytokines and cytokine receptors, the immune response. Academic Press 2006; 463-516.
54. Song M, Kellum JA. Interleukin-6. Crit Care Med 2005; 33: S463-5.
55. Hirano T, Akira S, Taga T, Kishimoto T. Biological and clinical aspects of interleukin 6. Immunol Today 1990; 11: 443-9.
56. Simpson RJ, Hammacher A, Smith DK, et al. Interleukin-6: structure-function relationships. Protein Sci 1997; 6: 929-55.
57. Chen D, Tang TX, Deng H, et al. Interleukin-7 biology and its effects on immune cells: mediator of generation, differentiation, survival, and homeostasis. Front Immunol 2021; 12: 747324.
58. Francois B, Jeannet R, Daix T, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight 2018; 3: e98960.
59. Levy Y, Lacabaratz C, Weiss L, et al. Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment. J Clin Investig 2009; 119: 997-1007.
60. Laing KJ, Secombes CJ. Chemokines. Dev Comp Immunol 2004; 28: 443-60.
61. Mukaida N. Chemokines. Reference Module in Biomedical Research 2014; 2014: 1056.
62. Hughes CE, Nibbs RJ. A guide to chemokines and their receptors. FEBS J 2018; 285: 2944-71.
63. Mollica Poeta V, Massara M, Capucetti A, Bonecchi R. Chemokines and chemokine receptors: new targets for cancer immunotherapy. Front Immunol 2019; 10: 379.
64. Remick DG. Interleukin-8. Crit Care Med 2005; 33: S466-7.
65. Erpenbeck VJ, Hohlfeld JM, Volkmann B, et al. Segmental allergen challenge in patients with atopic asthma leads to increased IL-9 expression in bronchoalveolar lavage fluid lymphocytes. J Allergy Clin Immunol 2003; 111: 1319-27.
66. Burleson SC, Fick RB, Mannie MD, et al. The immune basis of allergic lung disease. In: Comparative Biology Normal Lung. Parent RA (ed.). Academic Press 2015; 683-719.
67. Noelle RJ, Nowak EC. Cellular sources and immune functions of interleukin-9. Nat Rev Immunol 2010; 10: 683-7.
68. Kosaka S, Tamauchi H, Terashima M, et al. IL-10 controls Th2-type cytokine production and eosinophil infiltration in a mouse model of allergic airway inflammation. Immunobiology 2011; 216: 811-20.
69. KleinJan A, Dijkstra MD, Boksa SS, et al. Increase in IL-8, IL-10, IL-13, and RANTES mRNA levels (in situ hybridization) in the nasal mucosa after nasal allergen provocation. J Allergy Clin Immunol 1999; 103: 441-50.
70. Sun J, Madan R, Karp CL, Braciale TJ. Effector T cells control lung inflammation during acute influenza virus infection by producing IL-10. Nat Med 2009; 15: 277-84.
71. Brooks DG, Trifilo MJ, Edelmann KH, et al. Interleukin-10 determines viral clearance or persistence in vivo. Nat Med 2006; 12: 1301-9.
72. Ejrnaes M, Filippi CM, Martinic MM, et al. Resolution of a chronic viral infection after interleukin-10 receptor blockade. J Exp Med 2006; 203: 2461-72.
73. Blackburn S. Maternal, Fetal, & neonatal physiology-E-book: a clinical perspective. Elsevier Health Sciences 2017.
74. Leng SX, Elias JA. Interleukin-11. Int J Biochem Cell Biol 1997; 29: 1059-62.
75. Del Vecchio M, Bajetta E, Canova S, et al. Interleukin-12: biological properties and clinical application. Clin Cancer Res 2007; 13: 4677-85.
76. Dembic Z. Cytokines of the immune system: interleukins. The cytokines of the immune system the role of cytokines in disease related to immune response. San Diego: Mica Haley. 2015; 143-239.
77. Grencis RK, Bancroft AJ. Interleukin-13: a key mediator in resistance to gastrointestinal-dwelling nematode parasites. Clin Rev Allergy Immunol 2004; 26: 51-60.
78. Lacy P. Eosinophil cytokines in allergy. In: Cytokine Effector Functions in Tissues. Foti M, Locati M (eds.). Academic Press 2017; 173-218.
79. O'Shea JJ, Gadina M, Siegel RM. Cytokines and cytokine receptors. In: Clinical Immunology. Principles and Practice. Rich RR, Fleisher TA, Shearer WT, et al. (eds.). Elsevier 2019; 127-155.

80. Takashi K. Chapter 35. Hematopoietic Growth Factors. In: Handbook of Hormones. Comparative Endocrinology for Basic and Clinical Research. Takei Y, Ando H, Tsutsui K (eds.). Academic Press 2016; 314-5.
81. Secombes CJ, Wang T, Bird S. Vertebrate cytokines and their evolution. In: The Evolution of the Immune System. Conservation and Diversification. Malagoli D (ed.). Academic Press 2016; 87-150.
82. Yuzhalin AE, Kutikhin AG. The rest of interleukins. In: Interleukins in Cancer Biology. Yuzhalin AE, Kutikhin AG (eds.). Elsevier, Amsterdam 2015; 291-318.
83. Moghbeli M, Khedmatgozar H, Yadegari M, et al. Cytokines and the immune response in obesity-related disorders. Adv Clin Chem 2021; 101: 135-68.
84. Witowski J, Książek K, Jörres A. Interleukin-17: a mediator of inflammatory responses. Cell Mol Life Sci 2004; 61: 567-79.
85. Gracie JA, Robertson SE, McInnes IB. Interleukin-18. J Leukocyte Biol 2003; 73: 213-24.
86. Cen P, Walther C, Finkel KW, Amato RJ. Biomarkers in oncology and nephrology. Renal Disease in Cancer Patients. Finkel KW, Howard SC (eds.). Academic Press 2014; 21-38.
87. van Loo G, Bertrand MJ. Death by TNF: a road to inflammation. Nat Rev Immunol 2023; 23: 289-303.
88. Jang DI, Lee AH, Shin HY, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. Int J Mol Sci 2022; 22: 2719.
89. Popa C, Netea MG, Van Riel PL, et al. The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res 2007; 48: 751-62.
90. Silva LB, dos Santos Neto AP, Maia SM, et al. The role of TNF-α as a proinflammatory cytokine in pathological processes. Open Dentistry J 2019; 13: 332-8.
91. Clark DA, Coker R. Transforming growth factor-beta (TGF-beta). Int J Biochem Cell Biol 1998; 30: 293-8.
92. Marek A, Brodzicki J, Liberek A, Korzon M. TGF-beta (transforming growth factor-beta) in chronic inflammatory conditions-a new diagnostic and prognostic marker? Med Sci Monitor 2002; 8: RA145-51.
93. Bhattacharya P, Budnick I, Singh M, et al. Dual role of GM-CSF as a pro-inflammatory and a regulatory cytokine: implications for immune therapy. J Interferon Cytokine Res 2015; 35: 585-99.
94. World Health Organization. 2022.
95. Schuster M, Nechansky A, Kircheis R. Cancer immunotherapy. Biotechnol J 2006; 1: 138-47.
96. Dillman RO. Cancer immunotherapy. Cancer Biother Radiopharm 2011; 26: 1-64.
97. Mollica Poeta V, Massara M, Capucetti A, Bonecchi R. Chemokines and chemokine receptors: new targets for cancer immunotherapy. Front Immunol 2019; 10: 379.
98. Couzin-Frankel J. Cancer immunotherapy. Science 2013; 342: 1432-3.
99. Lee S, Margolin K. Cytokines in cancer immunotherapy. Cancers 2011; 3: 3856-93.
100. Kopf M, Bachmann MF, Marsland BJ. Averting inflammation by targeting the cytokine environment. Nat Rev Drug Discov 2010; 9: 703-18.
101. Berraondo P, Sanmamed MF, Ochoa MC, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer 2019; 120: 6-15.
102. Waldmann TA. Cytokines in cancer immunotherapy. Cold Spring Harb Perspect Biol 2018; 10: a028472.
103. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. Nat Rev Clin Oncol 2022; 19: 237-53.
104. Sportes C, Hakim FT, Memon SA, et al. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. J Exp Med 2008; 205: 1701-14.