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Immune System Disorders: Hypersensitivity and Autoimmunity

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Abstract

The immune response is known as a physiological mechanism to protect the body, providing defense to different systems that compose it and allowing its proper functioning. The ability to keep the organism free from foreign agents depends on the mechanisms of natural resistance or innate immunity, as well as the resistance that can develop over time through adaptive immunity. However, when these defense mechanisms fail, it can trigger injuries and diseases in the tissues, such as hypersensitivity, which is characterized as an excessive and undesirable reaction, produced by the immune system; as well as autoimmunity, which refers to the failure of the mechanisms of immunological tolerance, causing the reaction of the immune system against the body itself.

Keywords: innate immune response, adaptive immune response, histocompatibility, immune tolerance, hypersensitivity diseases, autoimmune diseases

1. Introduction

The immune system is characterized by both innate and adaptive immune responses. The innate response is characterized by the recognition of molecular patterns associated with damage and pathogens, whose molecules and receptors are fixed in the DNA of the germ line. Adaptive immunity is an antigen-specific response which is relatively slow, since it
requires a genetic rearrangement [1]. The main objective of the immune system is the defense against pathogens through these innate and adaptive mechanisms [2, 3]. However, dysfunction or deficiency of the immune system can lead to tissue injuries and diseases. On the one hand, there are hypersensitivity diseases, which are characterized by excessive and undesirable reactions, produced by the immune system [4]. On the other hand, autoimmune diseases refer to the failure of the immunological tolerance mechanisms, causing reactions against own cells and tissues [5].

2. Innate immune system

The innate immune system is the first line of defense against invading pathogens. It has a double role to provide initial control of the infection and initiate an adaptive immune response. The innate immune system consists of physical barriers such as epithelial layers and mucus, soluble factors such as the complement system, soluble mediators, cytokines and cells such as neutrophils, macrophages and dendritic cells [6]. These immune cells detected pathogens based on their molecules or pathogen-associated molecular patterns (PAMPs) that are recognized by multiple classes of pattern-recognition receptors (PRRs) that initiate inflammatory responses [7]. PRRs can also recognize host molecules containing damage-associated molecular patterns (DAMPs), molecules that are released from cells damaged [8]. Then, these PRRs respond by producing several soluble mediators such as the complement system and proinflammatory cytokines to kill microbes or infected cells [1].

2.1. Immune innate system cells

The cells of the innate immune system have several functions that are essential for the defense of the organism. These cells respond by producing inflammatory cytokines and some of them are responsible for removing foreign substances, pathogens or infected cells. Some of the innate immune cells include macrophages, dendritic cells, neutrophils, mast cells, basophils and eosinophils.

2.1.1. Macrophages

Macrophages function as cells that capture and degrade agents that are not recognized as belonging to the organism, in addition to being antigen-presenting cells; therefore, they are essential in both types of immunity (innate and adaptive) [9]. Macrophages are formed in the bone marrow from myeloid progenitor cells, which when stimulated by the granulocyte-macrophage colony-stimulating factor (GM-CSF) are converted into monocytes, immature cells that are released into the bloodstream. Monocytes mature when stimulated by chemotactic substances, making them migrate to tissues as mature cells, establishing themselves for a lifetime of weeks to months. This cell type is directly related to the inflammatory response, since phagocytosis uses harmful substances that can cause acute cell injury and promote apoptosis, including reactive oxygen species (ROS), high amounts of nitric oxide and halogenating radicals. Other mechanisms that promote inflammation are through the production of cytokines such as interleukin (IL)-6.
and tumor necrosis factor (TNF)-α. However, it has also been seen that macrophages modulate inflammation through the release of anti-inflammatory cytokines and growth factors such as IL-10, vascular endothelial growth factor (VEGF)-α, transforming growth factor (TGF)-β and Wnt proteins [10, 11]. Then, the macrophages can be divided into two general classes, depending on their phenotype, M1 that promote inflammation and M2 that release anti-inflammatory and pro-regenerative cytokines [12, 13].

2.1.2. Dendritic cells

The process of formation of dendritic cells (DCs) is like macrophages, being monocytes in their more immature stage. However, these cells are directed to epithelia even as immature cells and remain there for long periods (weeks or months). When they capture microorganisms or antigenic agents, they eliminate them by phagocytosis, going through the lymph to the lymph nodes, where they will perform their specialized function as antigen-presenting cells [14]. The DCs present antigens to the T lymphocytes; however, it has been proven that they are also capable of activating B lymphocytes, natural killer (NK) cells, macrophages and eosinophils. DCs participate in innate immunity; however, they regulate the adaptive immune response and are fundamental for the development of immunological memory and tolerance [15]. There are mainly two DCs subpopulations: classical and plasmacytoid DCs. On the one hand, classical DCs are specialized cells in the antigen processing and presentation, which have both high phagocytic activity and capacity for cytokine production [16]. On the other hand, plasmacytoid DCs are long-lived cells [17], which are present in the bone marrow and in all peripheral organs and are specialized to respond to viral infection with mass production of type I interferons (IFN). However, these DCs can also act as antigen-presenting cells and control the responses of T cells [18].

2.1.3. Neutrophils

Neutrophils are phagocytes that are derived from myeloid cells as well as monocytes and dendritic cells. Its morphology is very characteristic, since they present nuclear lobes of different morphologies and they are known as polymorphonuclear (PMN). It is the most abundant leukocyte in the blood (up to 70% of the total of leukocytes) and unlike the other phagocytes, neutrophils are released into the blood as mature cells; however, they have a short life time (from hours to maximum 2 days). They are the first cells of the immune system to reach the focus of infection and their function is practically phagocytosis. Although its short life has been identified that neutrophils are also involved in adaptive immunity, previously, it was known that neutrophils participated in the elimination of foreign agents by phagocytosis, dying in their function; however, it has been found that neutrophils have the ability to return to the bloodstream as antigen-presenting cells, interacting with dendritic cells, NK cells, T and B lymphocytes [19, 20].

2.1.4. Mast cells

Mast cells are derived from mesenchymal precursor cells (MCPs) in bone marrow but mature in peripheral tissues. They are distributed mainly in tissues close to the external environment such as the skin, mucous membranes, digestive tract and respiratory tract. Activation of mast
cells is practically due to the binding of immunoglobulin (Ig)-E antibodies to the high-affinity receptors for the Fc region of IgE (FcεRI) found in their plasma membrane, triggering the release of their granules containing high concentrations of histamine, tryptase, chymase, carboxypeptidase and heparin [21]. Activation of mast cells causes the activation of phospholipase A2 and breaks down membrane lipids to produce arachidonic acid, which can be metabolized in two ways: (1) the cyclooxygenase (COX) pathway, producing prostaglandins and (2) the lipoxygenase pathway (LOX), producing leukotrienes. Both prostaglandins and leukotrienes have pro-inflammatory effects, increasing vascular permeability. The mast cells boost the immune response, increasing the recruitment of specific cells against pathogens, activating different types of immune cells such as macrophages, eosinophils and lymphocytes that eliminate bacteria, fungi, some parasites and cells infected by viruses. Mast cells activate other cells of the immune system by releasing TNF-α, TGF-β, IL-4, IL-5, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), VEGF and fibroblast growth factor (FGF)-2 [22].

2.1.5. Basophils

Basophils are granulocytes derived from myeloid cells. They are the least abundant (0.5% of leukocytes) and have a nucleus in the form of S, lobed (1–3 lobes). They have many granules containing histamine, heparin, serotonin and high amounts of leukotrienes. Like mast cells, they contain histamine in their granules, being responsible for most of the early symptoms of IgE-dependent and non-dependent allergy (sneezing, pruritus, bronchospasm and edema). Basophils migrate to the site of inflammation and secrete proteases and various inflammatory mediators such as IL-4 to activate cells such as macrophages, innate lymphoid cells, fibroblasts and endothelial cells, aggravating the allergic inflammatory response [23, 24].

2.1.6. Eosinophils

Eosinophils are bilobed granulocytes originating from the bone marrow from myeloid cells, being released into the bloodstream in a mature manner and at low concentrations (3% of the total of granulocytes). An important characteristic of eosinophils is their high quantity of granules, which have different components, among which are high concentrations of leukotrienes, ROS, IL-4, IL-5, neurotoxins (EDN), main basic protein (MBP), eosinophilic cationic protein (ECP) and eosinophilic peroxidase (EPO) [25, 26]. Eosinophils play an important role in hypersensitivity since they are stimulated by IL-5 produced by mast cells and Th2 cells. Also, fibroblasts when stimulated by IL-4, release eotaxins, molecules that stimulate the function of eosinophils [27].

2.2. Pattern recognition receptors

Innate immune cells are capable of recognizing pathogens and endogenous molecules of proteins known as PRRs. These receptors recognize highly conserved motifs known as PAMPs or DAMPs. PRRs dictate the initiation of an adequate and effective innate immune response, as well as the activation of the adaptive immune response to infection or inflammation [28]. These PRRs include Toll-like receptors (TLRs), nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs) and RIG-I-like receptors (RLRs) [29].
The TLRs family, was originally identified in Drosophila, as important genes for its ontogeny and the innate immune response in Drosophila adults [30]. The TLRs family consists of 10 highly conserved transmembrane glycoproteins in humans, which recognize a wide range of pathogens [31]. TLR-1, TLR-2, TLR-4, TLR-5, and TLR-6 are expressed on the cell surface, while TL-3, TLR-7, TLR-8, and TLR-9 are found intracellularly in endosomes [32]. The extracellular leucine-rich repeat (LRR) regions in the TLRs mediate protein-protein or PAMP-protein interactions, while their intracellular tails mediate proinflammatory signaling through the myeloid differentiation primary response protein (MYD88) and TIR domain-containing adapter molecule 1 (TRIF; also known as TICAM1) pathways [33]. They are expressed in a wide variety of cells such as innate immune cells, T and B cells, epithelial cells, fibroblasts, and endothelial cells; however, not all cell types express every TLR [34]. Different TLRs specifically recognize distinct PAMPs and DAMPs [35]. For example, TLR2 recognizes lipoarabinomannan from mycobacteria [36]. Some TLRs detect different nucleic acids; TLR3 detects viral double-stranded RNA (dsRNA) formed during the replication of positive stranded viral RNA in the cytosol [37]; TLR7 and TLR8 both recognize viral single-stranded RNA (ssRNA) [38, 39] and TLR9 recognizes bacterial DNA [40]. TLR4 together with myeloid differentiation factor (MD)-2 recognizes lipopolysaccharide (LPS), which comes from Gram-negative bacteria [41]. Further, TLR4 is also involved in antiviral innate immunity [42, 43]. TLR5 is highly expressed DCs and detects bacterial flagellin [44, 45]. Plasmacytoid DCs express TLR7 and TLR9, and both are implicated in recognition of viral and bacterial nucleic acids [46]. TLR10 has been implicated in the recognition of Helicobacter pylori by gastric epithelial cells and may act as a heterodimer with TLR2 [47, 48].

The NLR family comprises 22 members in humans. Most NLRs share common structural characteristics including a C-terminal leucine-rich repeat (LRR) domain, often involved in ligand recognition, a central NOD, and a variable N-terminal effector domain [49]. Based on the type of effector domains that is either a caspase recruitment domain (CARD), a pyrin domain (PYD), or a baculoviral inhibitor of apoptosis protein repeat (BIR) domain [50], the NLR family can be categorized structurally into five subsets based on their N-terminal effector domain: NLRA, NLRB, NLRC, NLRP and NLRX [29]. The most well-defined sensors of peptidoglycan are the cytosolic NOD-like receptors (NLRs), NOD1 and NOD2, which are expressed by diverse cell types, including myeloid phagocytes and epithelial cells [51], which recognize specific ligands from various pathogens. This family is involved in increasing the proinflammatory events caused by cell death and several more proinflammatory processes [52].

The RIG-I-like receptor family consists of RNA-binding proteins that are expressed in almost all cells. Family members include RIG-1, melanoma differentiation-associated gene (MDA)-5, and laboratory of genetics and physiology (LGP)-2 [34]. They act as sensors for viral replication within human host cells necessary to mediate antiviral responses [53].

2.3. Cytokines

Cytokines are secreted proteins that can be delineated as a distinct class of signaling molecules from hormones based on two key factors. First, the kinetics of cytokine secretion (rapid and dramatic induction following specific extracellular stimuli), which is often prolonged at less dramatic concentrations to affect physiological changes. Second, cytokines can be signaling autocrine, paracrine and endocrine fashions [54, 55]. Cytokines are involved in regulating
the homeostasis of the organism, but when its production or its signaling pathway in the cell is not regulated, this homeostasis is altered, which can trigger in a pathology [56, 57].

Cytokines can be classified into five groups [57]: (1) IL-1 superfamily, there are 10 members of the IL-1 family of receptors (IL-1R1–ILR10) [58] and 11 members of the IL-1 family of cytokines (IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-37 and IL-38) [59]. The interleukin-1 superfamily members are closely linked to damaging inflammation; however, the same members also function to increase nonspecific resistance to infection and the development of an immune response to foreign antigens [60]. (2) TNF superfamily is composed of 19 ligands and 29 receptors [61]. This family plays a pivotal role in immunity, inflammation and controlling cell cycle (proliferation, differentiation and apoptosis) [62]. (3) The interleukin (IL)-17 cytokine family is composed of IL-17A and five other members (IL-17B, IL-17C, IL-17D, IL-17E, also referred to as IL-25, and IL17F). IL-17-related cytokines play key roles in defense against extracellular pathogen, autoimmune. In addition, there is evidence that indicates that some of these molecules are involved in the amplification and perpetuation of pathological processes in many inflammatory diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis and allergy. However, the same cytokines can exert anti-inflammatory effects in specific settings and play key role in the control of immune homeostasis [63, 64]. (4) IL-6 superfamily is comprised by IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin (CT)-1, IL-11, cardiotrophin-like cytokine factor (CLCF)-1, viral IL-6 (vIL-6), IL-27 and IL-35 [65]. This cytokine family shows some redundant but not uniformly identical biological activity. IL-6 exerts pleiotropic effects on inflammation, immune response and hematopoiesis [66, 67]. IL-6 is produced at the inflammation site by infection or tissue damage, which induces production of acute phase proteins such as C-reactive protein (CRP), serum amyloid A, fibrinogen and hepcidin in liver. IL-6 also plays an important role in acquired immune response to induce differentiation of activated B cells in to antibody (Ab)-producing cells and to prolong survival of plasmablasts [65], while it promotes the development of Th17 cells and follicular helper T cells by naïve T cells and inhibits the differentiation into regulatory T cells (Treg) [68]. But, dysregulated excessive or persistent production of IL-6 plays a pathological role in various kinds of diseases [65]. (5) Type I superfamily, includes the common γ-chain cytokines (IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 and IL-21) [69], common β-chain cytokines (IL-3, IL-5, GM-CSF) [70] and IL-12 subfamilies (IL-12, IL-23, IL-27 and IL-35), as well as similar cytokine products with unique receptor characteristics such as IL-13, IL-14, IL-32, IL-34, granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF). (6) Type II superfamily contains the interferons (type I, II and III) and the IL-10 subfamily (IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26) [54].

2.4. Inflammatory response and phagocytosis

Inflammation is a protective response to infection, tissue stress and injury [71]. This inflammatory response is characterized by its clinical signs such as redness, heat, swelling, pain and dysfunction [72]. The inflammatory response is triggered by inducers such as PAMPs derived from bacteria, viruses, fungi and parasites; and DAMPs derived from cell damage, as well as toxic cellular components or any other harmful conditions [73]. Then, these inflammatory inducers are detected by “sensors,” which are present in several immune cells. These sensors are PRRs such as TLRs, NLR and RIG-like receptors [52, 74]. Subsequently, the PRRs induced
the synthesis and release of soluble mediators such as cytokines [75]. Cytokines, as optimal protection against pathogens, provide the necessary signals to initiate an inflammatory response, through the differentiation and proliferation of the immune system cells, adapting their effector functions as necessary to promote protective immunity, and once the inducers are eliminated, they suppress the inflammatory response, promoting tissue repair and return to homeostasis [54]. The inflammatory response is characterized by successive phases [76]: (1) silent phase, where cells reside in the damaged tissue releases in the first inflammatory mediators; (2) vascular phase, where vasodilation and increased vascular permeability occur; (3) cellular phase, which is characterized by the infiltration of leukocytes to the site of injury; and (4) resolution of inflammation, which is the process to return tissues to homeostasis [77–79].

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4. Resolution of inflammation, which is the process to return tissues to homeostasis.

Phagocytosis is the physiological process carried out by phagocytic cells to identify, digest and eliminate foreign substances or pathogens (Figure 1). Infection with pathogens is the most common cause to trigger this immune mechanism. The pathogens proliferate releasing small peptides with chemotactic activity, dispersing in the areas of underlying tissue and blood vessels. These chemotactic peptides come into contact with the endothelial cells that form the blood vessels and phagocytes that are found in the invaded tissue (macrophages and/or dendritic cells), as well as those found in the blood (neutrophils and monocytes). Endothelial cells initiate the synthesis of cell adhesion proteins, as do phagocytes found in the blood. The adhesion proteins allow the phagocytes of the blood to bind to the endothelial cells, causing them to roll on the surface until finding an exit between the cell junctions, migrating to the extravascular space by a process known as diapedesis. The phagocytes that were close to the area of infection and those that migrated from the blood move toward the focus of infection attracted by the chemotactic peptides. The microorganisms have structural components (the receptor for IgG (FcR) and PAMPs, among others) that are recognized by PRRs found in phagocytes [80, 81].

The interaction of these surface molecules causes the invagination of the cell membrane and the formation of cellular prolongations that end up involving the foreign pathogens in a phagocytic vacuole or phagosome. The chemical interaction of the molecules on the membrane surface of microorganisms and phagocytes activates diverse receptors, including those of Gq proteins that activate phospholipase C, an enzyme that degrades membrane phospholipids to produce inositol trisphosphate (IP3) and diacylglycerol (DAG). The IP3, among many of its functions, is responsible for regulating cell movement through the cytoskeleton by the release of calcium ions by the endoplasmic reticulum. On the other hand, the DAG activates a protein kinase C (PKC), which activates the cytosolic proteins p40, p47 and p67, which are supported by ras-related protein Rap-1A (RAP1A), interact with cytochrome B558, one of the components of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Activated NADPH oxidase promotes the release of ROS, molecules highly toxic to cellular components. NADPH oxidase captures high amounts of oxygen, transforming them into superoxide anions (O2−), which in turn promote the formation of dangerous ROS such as hydrogen peroxide (H2O2), hydroxyl (OH−) and oxygen singlet (‘O2). The ROS react with the biomolecules of the plasma membrane causing the death of the microorganisms (lipids, polysaccharides, proteins and nucleic acids), causing their death. Simultaneously, the phagocytes fuse lysosomes to the vacuole in which the microorganism is internalized, forming the phagosome, also releasing many hydrolytic enzymes that favor the digestion of the microorganism components [82].
Lysosomes contain myeloperoxidase, an enzyme that hydrolyzes hydrogen peroxide for the formation of halogenating radicals such as hypochlorous acid, hypochlorite and hypoiodite, which increase the damage to microorganisms. Finally, cell debris has two purposes: (1) to be eliminated by exocytosis, (2) to transport certain antigenic components to the cell membrane to be presented to T and B cells and be able to give the process of acquired immunity (mainly in the case of dendritic cells and macrophages) [82].

3. Adaptive immune system

The adaptive immune system has the capacity to generate a wide range of specific antigen receptors, through somatic mechanisms of gene rearrangement. These mechanisms create a
random repertoire of receptors that are clonally distributed in T and B lymphocytes. This gives it the advantage of having a wide repertoire of specific antigen receptors, which can be recognized, without these having to be encoded in the host genome, allowing the recognition of almost any antigenic structure. The activation of lymphocytes requires two types of signals: (1) a signal induced by the antigen receptor itself when recognizing its related antigen, and a costimulatory signal by professional antigen-presenting cells (APCs). Therefore, the innate immune system, as already explained earlier, determines the origin of the antigens by means of a non-clonal system of receptors, PRRs, encoded in the germ line, which controls the expression of costimulatory molecules and effector cytokines, while the adaptive immune system does it through antigenic receptors [83, 84].

3.1. T lymphocytes

During the hematopoiesis that is generated in the bone marrow, it gives rise to the precursors of all the lineages and states of differentiation of the T cells. These precursors, called thymocytes, travel through the peripheral blood and reach the thymus, where they mature in T lymphocytes. Later, they will differentiate into CD4⁺ T lymphocytes (cooperators) or CD8⁺ T lymphocytes (cytotoxic). Once they are differentiated, they travel through the blood circulation until they are activated by means of the surface receptor they present, when they encounter a specific antigen. This receptor, known as T cell receptor (TCR), binds to the major histocompatibility complex (MHC), a complex expressed by antigen-presenting cells, in which the antigen is presented in the form of peptides. Depending on the T cell to which the antigen is presented, MHC class I or MHC class II will be used. To present an antigen to the CD4⁺ T lymphocyte, a presentation through the MHC-II will be required; while for the activation of a CD8⁺ T lymphocyte, it will be necessary through the MHC-I [84, 85]. T lymphocytes are responsible for cellular adaptive immunity. The activation of CD8⁺ T lymphocytes allows the destruction of infected cells through the release of perforins, which are proteins responsible for forming pores in the membrane of the target cell that causes the passage of water and ions, inducing an osmotic lysis of the infected cell. Similarly, CD8⁺ T lymphocytes release toxic enzymes such as the granzyme that passes through the pores formed in the cell membrane, which causes the induction to cell death by fragmenting the DNA of the infected cell. Activation of CD4⁺ T lymphocytes allows cooperation with other immune cells for their activation. As the case of macrophages, B lymphocytes and other T lymphocytes, through costimulatory molecules and the release of cytokines, this causes a powerful cellular activation and therefore an effective immune response. In addition to this, CD4⁺ T lymphocytes can differentiate into cellular subpopulations with specific action. Mediated by the secretion of cytokines, they can be differentiated into Th1, Th2, Th9, Th17 and Th22 types [86].

In addition, memory T lymphocytes have a long life, functionally inactive but respond to new exposures of the same antigen quickly and efficiently. There is another population of T lymphocytes, the regulatory T lymphocytes [86]. This cellular population is responsible for eliminating autoreactive T cells that escaped the process of negative selection or central tolerance; with the purpose, to avoid the development of an autoimmune response [87]. Other lymphocytes, such as LTγ/δ, are another very rare cell type that represent about 10% of intraepithelial lymphocytes of the small intestine but increase drastically under certain
allergic or inflammatory conditions. In addition, they recognize complete proteins without needing to be processed to be presented through the MHC molecules [88].

3.2. B lymphocytes

The B lymphocytes are originated from the same precursor that gives origin to the T lymphocytes and the NK cells. However, the absence of certain cell membrane receptors in B lymphocytes leads to their differentiation in this cell line, a process that takes place in bone marrow. Up to this point, the B lymphocytes are immature, and it will be until they migrate from the bone marrow into the spleen to undergo positive and negative selection and thus produce a mature B lymphocyte [89]. B lymphocytes can be activated: (1) by a foreign agent through the TCD4+ lymphocytes collaboration; (2) or in specific circumstances independent of CD4+ T lymphocytes. In the case of CD4+ T lymphocytes collaboration, it occurs through the MHC expressed in its cell membrane, which binds to the B cell receptor (BCR), to initiate the antigenic presentation that will end in the synthesis of antibodies [90]. B lymphocytes are cells that participate in humoral adaptive immunity, since once activated they proliferate in response to the antigen and differentiate into plasma cells to produce antibodies against the specific antigen [91]. Likewise, activated B lymphocytes can differentiate into memory cells, acquiring a capacity for survival for long periods of time, up to more than 10 years, approximately [92, 93]. However, various co-stimulatory receptors that are expressed in B cells can induce their proliferation and survival, as well as the regulation of the production of specific antibodies that contribute to a breakdown of immunological tolerance, triggering autoimmune diseases [94].

3.3. Antibodies

Antibodies, also known as immunoglobulins (Ig) are structurally composed of two heavy polypeptide chains identical to each other and two light chains also identical, joined by one or more disulfide bridges. They have a variable region with two domains (VH, VL) and a constant region with four domains (CL, CH1, CH2 and CH3) [95]. The segments of the variable region originate through a somatic recombination, which allows having the diversity in the repertoire of antibodies, since at least 1026 of different specific antibodies are generated. They have a Fab fragment (fragment antigen binding) and an Fc fragment (crystallizable fraction). The Fab portion is an antigen-binding zone, while the Fc is a constant zone where the interaction with cellular receptors and the effector part of the biological functions presented by the antibodies occurs. Among these biological functions are crossing the placental barrier, activating complement, neutralizing antigens, joining phagocytic cells and acting as opsonin; all to generate protection and eliminate pathogens or elements harmful to the host [96].

There are 5 classes recognized up to the moment of antibodies: IgA, IgG, IgM, IgE and IgD. Most are monomeric, but they can be presented pentameric as IgM and only IgA can be present in both dimeric and monomeric forms. There are 4 subclasses for IgG (IgG1-IgG4) and 2 for IgA (IgA1 and IgA2). This is due to variations in the constant regions, which causes functional differences between the antibodies of the same class [97]. Among the functions of IgG is complement activation, with subclass IgG3 having the greatest effect, whereas IgG4
cannot activate it. It is the antibody in greater amount circulating in the blood and more increases during a secondary immune response. It can cross the placenta and, in the newborn, favors its immunological protection. It helps in phagocytosis through opsonization, as well as in the neutralization of pathogens with great effectiveness [98]. IgA is found in greater concentration due to its location in epithelia, in body secretions such as saliva, tears, colostrum, respiratory, gastrointestinal and genitourinary secretions; which allows it to generate a broad protection against pathogens and allergens. In blood circulation, it is found in a monomeric way; but in mucous, it is found in a dimeric form behaving as secretory IgA [99]. The IgE antibody is found in very small concentrations in the bloodstream. The majority is bound to a surface receptor of mast cells, eosinophils and basophils, which causes it to be involved in allergic reactions in humans, since it induces the release of pro-inflammatory cytokines when IgE recognizes specific antigens [100]. It also causes degranulation of the aforementioned cells, causing the release of vasoactive substances such as histamine, causing an inflammatory response. Also, it can increase the production of this antibody by the effect of allergens such as those that can be found in food, some drugs and seasonal allergens, which causes allergic reactions. This immunoglobulin is very effective in the defense against parasitic infections [101]. In the case of IgM, it is the first antibody that appears with immune response reactions. It is the first antibody that is expressed on the surface of B lymphocytes and the one that predominates in primary immune reactions. It is the largest, due to its pentameric formation, which allows it to bind several antigens (approximately, 6 antigens per IgM) and is the main activator of the complement system [102]. Finally, IgD is the immunoglobulin that is also found on the surface of B lymphocytes, being a marker of their maturity. However, at the time of contact with the antigen, IgD is lost during antigenic stimulation. It participates as an antigen receptor and signaling transmitter inside the cell and, in blood circulation, it is found in very small amounts and is not produced by plasma cells [103].

4. Histocompatibility

The molecules of the major histocompatibility complex (MHC), also called human leukocyte antigens (HLA) [104, 105], are the product of a set of genes responsible for the lymphocytes rejecting transplanted tissues and detecting foreign elements. These molecules also participate in the induction of the specific immune response, through the presentation of the antigen to the T lymphocytes [104]. In the mammalian genome and, more specifically, in the human genome, the most variable region known forms the MHC that carries a great number of different loci coding for functional genes [106]. The classical MHC encompasses approximately 3.6 megabase pairs (Mb) and is divided into three subregions: the telomeric class I, class III, and the centromeric class II regions [107]. In humans, the MHC region is approximately 4000 kb long, located on the short arm of chromosome 6 [105, 106].

Molecular markers, located on the cell surface, help to externalize the intracellular environment and give the individual a specific tissue identity, recognized by their immune system. Under normal conditions, the MHC molecules reach the cell membrane bound to their own elements, so when they are presented to the T lymphocytes, they do not activate them; when
by infection or pathological changes of the cell, they emerge, carrying a foreign molecule instead of their own, the T cell is activated and responds immediately [108]. The function of MHC molecules is to bind peptide fragments derived from pathogens and display them on the cell surface for recognition by the appropriate T lymphocyte. The consequences are almost always deleterious to the pathogen—virus-infected cells are killed, macrophages are activated to kill bacteria living in their intracellular vesicles, and B lymphocyte are activated to produce antibodies that eliminate or neutralize extracellular pathogens [105].

4.1. Major histocompatibility complex (MHC-I)

The genes, whether expressed, are arranged in three genomic regions or classes. The more distal region corresponds to MHC class I, which carries the genes that code for the classic (1a) class I HLA-A, -B, and -C heavy chains, all nucleated cells express class I molecules on their cell surface [109]. They present cytoplasmic or endogenous antigens (synthesized intracellularly, those of viral or tumoral origin and processed by the proteasome) to the CD8$^+$ T lymphocyte [110]. MHC-I is a molecule made up of an α polypeptide chain, with three domains (α1, α2 and α3) and the β$_2$ microglobulin subunit. In the clef that is formed between α1 and α2, it is added the antigenic peptide that is going to present [108]. The classical molecules MHC-I (A, B and C) are expressed on the surface of all cells, except those of the trophoblast, erythrocytes and neurons. Its main function is the presentation of antigens to the CD8$^+$ T lymphocyte [111]. MHC-I is formed in the endoplasmic reticulum and interacts with the chaperone molecules: calnexin and calreticulin, which help it to bind with the β$_2$ microglobulin and confer stability on it. A third molecule, the capsid, helps transporting antigen processing peptides (TAP)-1 and TAP2 to form the channel that allows the passage of the antigenic peptide from the cytoplasm to the endoplasmic reticulum, where it binds to the MHC-I. This complex (MHC-I-antigenic peptide) leaves the endoplasmic reticulum in a vesicle, travels through the cytoplasm and is finally exocytosed. On the cell surface, the MHC molecule and the antigenic peptide that it carries bind to the CD8$^+$ T lymphocyte receptor and it is through this union that the so-called “presentation” is made. If the presented peptide corresponds to a molecule of its own, the lymphocyte does not respond. If the presented peptide is foreign, accessory signals are transmitted through costimulatory molecules such as B7-CD28, CD40-CD40L, etc., which activate CD8$^+$ T lymphocyte. The activated cytotoxic lymphocyte, through the firing of cytolytic enzymes and the induction of apoptosis, destroys the host cell, carrier of endogenous antigens such as viruses or tumor cell elements (Figure 2, right) [108].

4.2. Major histocompatibility complex (MHC-II)

The MHC class II genes, coding for both chains that will form the functional heterodimer, HLA-DR, HLA-DQ, HLA-DP, HLA-DM, and HLA-DO are in the more centromeric portion of the MHC region [109]. They exhibit restricted expression, being predominantly expressed on antigen-presenting cells (APC), such as macrophages, DCs, Langerhans and Kupffer cells, as well as B lymphocytes [112], also intravesicular or exogenous antigens (synthesized extracellularly and processed by lysosomes) to CD4$^+$ T lymphocyte [110]. CMH-II is composed of two polypeptide chains: α and β, both with two domains. The antigenic peptide binding site it presents is located between α1 and β1 [105, 108]. The antigen, for its presentation, must be processed by the cell that captured it and be reduced to small peptides, since the sites to which
it binds both in the MHC and in the T lymphocyte, can only host molecules with a smaller size to 25 amino acids [108]. The classical molecules MHC-II (DP, DQ and DR) are expressed, constitutively, on the surface of the cells participating in the “immune response” (phagocytes and lymphocytes), but by activation with INF-γ, they can be expressed in other cells that, like fibroblasts, keratinocytes, barley and endothelial, also participate in this response [111]. The MHC-II is synthesized in the endoplasmic reticulum and portal a molecule: the invariant chain (Li or CD74) that protects the site that the antigen will occupy, favors its exit of the reticulum and takes it to endosomes where it meets the antigenic peptides. In this place, various cathepsins break the Li chain, which leaves the site corresponding to the antigen free and allows its binding to MHC, the Li residues (CLIP) are removed by the DM molecule. Finally, the antigenic peptide emerges to the surface linked to MHC-II, a molecule through which it makes contact and is presented to the CD4+ T lymphocyte. If the presented molecule is strange, the T-helper cell cytokines are activated and secreted. These cytokines can activate the host cell and lymphocytes and cells surrounding (Th1 predominant response), as well as stimulate the production of antibodies (Th2 predominant response). The class of secreted cytokines and therefore, the function that they do, depends on the type of Th cell that responds. In all cases, there is a regulation that, at the end of the Antigenic stimulus: slows the response, induces apoptosis activated cells, inhibits inflammation and initiates repair (Figure 2, left) [113].

5. Immune tolerance

5.1. Central tolerance of lymphocytes T and B

The “immunological tolerance” was established in 1954, as an acquired state learned during the development of the immune system by exposure to antigens in its immediate environment [114].
A single antigen can induce an immune response or tolerance depending on the context in which it occurs. Tolerance is acquired, triggered from the ontogeny of lymphocytes and there are different mechanisms to maintain it. One is carried in the primary lymphoid organs, known as central tolerance. The other is carried in the secondary lymphoid organs and is known as peripheral tolerance [115]. The central tolerance, also known as negative selection, is carried out during the development of the T and B cells, when the newly generated cells test their receptors for the recognition of antigens in their immediate environment. It consists of a clonal elimination in the bone marrow of autoreactive B lymphocytes and self-reactive T lymphocytes in the thymus. It prevents maturation of those lymphocytes capable of recognizing autoantigens through the expression of high affinity receptors and occurs through the recognition of these by the antigen-presenting cells through MHC molecules. On the other hand, peripheral tolerance allows maintenance in the control of effective immune responses against “self” [116].

5.2. Peripheral tolerance of T and B lymphocytes

After the T and B lymphocytes have passed through the control of negative selection or central tolerance and mature, they are directed by blood circulation to secondary lymphoid organs such as the spleen and lymph nodes. Lymphocytes require secondary signals to activate and generate a positive response against foreign antigens. If the lymphocytes do not generate a positive response against these antigens, the lymphocytes become anergic or die by apoptosis. Similarly, when lymphocytes are activated by antigens inappropriately (autoactive), regulatory mechanisms are activated that correct such failures through the participation of regulatory T lymphocytes (Tregs) [117].

5.3. Tolerance induced by exogenous antigens

The tolerance for exogenous antigens is due to the lack of immune response against antigens from food and normal flora, as well as inhaled antigens, to avoid triggering an immune response that affects the integrity of the individual. This type of tolerance occurs mainly on mucous membranes. The participation of IgA immunoglobulin as essential component of mucosal immunity, whose function is the neutralization of antigens or immune complexes, prevents their absorption and progression of active immune response. Dendritic cells are also highly responsible for immunological tolerance toward exogenous antigens. In part, they are responsible for their ability to induce the expression of Tregs FOXP3⁺ lymphocytes [118].

6. Immune hypersensitivity

The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the host. Hypersensitivity diseases include autoimmune diseases, in which immune responses are directed against self-antigens, and diseases that result from uncontrolled or excessive responses to foreign antigens. Because these reactions tend to occur against antigens that cannot be escaped (i.e., self-antigens) and because of positive feedback systems intrinsic to
various aspects of the immune response, hypersensitivity diseases tend to manifest as chronic problems. The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system (Figure 3) [119].

6.1. Type I reactions

Immediate hypersensitivity reactions are mediated by IgE, but T and B cells play important roles in the development of these antibodies. The allergic reaction first requires sensitization to a specific allergen and occurs in genetically predisposed individuals. The allergen is either inhaled or ingested and is then processed by APC, such as a DCs, macrophage, or B-cell [120]. The APC then migrates to lymph nodes, where they prime naïve T cells that bear receptors for the specific antigen. After antigen priming, naïve T cells differentiate into Th1, Th2, or Th17 cells based upon antigen and cytokine signaling. In the case of allergen sensitization, the differentiation of naïve T cells is skewed toward a Th2 phenotype. These allergen-primed Th2 cells then release IL-4, IL-5, IL-9 and IL-13. IL-5 plays a role in eosinophil development, recruitment and activation. IL-9 plays a regulatory role in mast cells activation. IL-4 and IL-13 act on B cells to promote production of antigen-specific IgE antibodies. For this to occur, B cells must also bind to the allergen via allergen-specific receptors. They then internalize and process the

Figure 3. Hypersensitivity reactions. (A) Type I hypersensitivity. The binding of the antigen to preformed IgE antibodies bound to the surface of mast cells or basophils, causes the release of inflammatory mediators such as histamine, cytokines and metabolites of arachidonic acid, which produces clinical manifestations, such as septic shock, rhinitis allergic, allergic asthma and acute allergic reactions to drugs. (B) Type II hypersensitivity. Cytotoxic reactions involve the binding of both IgM and IgG antibodies to antigens bound to cells. The antigen–antibody binding results in the activation of the complement cascade and in the destruction of the cell to which the antigen is bound. (C) Type III hypersensitivity. Immunocomplexes are formed when the antigens bind to the antibodies. They are usually removed from the process by phagocytosis. However, the deposition of these immunocomplexes in the tissues or in the vascular endothelium can produce a tissue aggression mediated by immunocomplexes. (D) Type IV hypersensitivity. These types of reactions are not mediated by antibodies. Delayed hypersensitivity reactions are mediated primarily by T lymphocytes (cell-mediated immunity).
antigen and present peptides from it, bound to the MHC-II molecules found on B cell surfaces, to the antigen receptors on Th2 cells. Type I reactions are immediate hypersensitivity reactions involving IgE-mediated release of histamine and other mediators from mast cells and basophils (Figure 3A). Examples include anaphylaxis and allergic rhinoconjunctivitis [121].

6.2. Type II reactions

Type II or cytotoxic hypersensitivity [119] depends on the abnormal production of IgG or IgM directed against tissue antigens or a normal reaction to foreign antigens expressed on host cells. There are three main mechanisms of injury in type II reactions: (1) activation of complement followed by complement-mediated lysis or phagocytosis and removal by leukocytes; the IgG or IgM antibody can complex with antigens on the surface of cells or extracellular matrix and this complex then may activate complement. Complement activation will result in formation of the membrane attack complex (MAC) and cause osmotic lysis of the target cell; (2) antibody-dependent cellular cytotoxicity; the second type II reaction is called antibody-dependent cell-mediated cytotoxicity IgG antibodies that can bind FcγRIII on NK cells and macrophages, thus mediating the release of granymes and perforin and resulting in cell death by apoptosis (ADCC); (3) inactivation of a biologically active molecule; disruption of biologically functional molecules can occur when autoantibodies bind to these molecules (Figure 3B). An example is antibody produced against acetylcholine receptors in myasthenia gravis resulting in increased turnover of the receptor at motor end-plates and subsequent muscular weakness or drug-induced hemolytic anemia [122, 123].

Drug-induced immune hemolytic anemia (DIIHA) is rare, and required to provide the optimal serological tests to confirm the diagnosis. The drugs most frequently associated with DIIHA at this time are cefotetan, ceftriaxone and piperacillin. DIIHA is attributed most commonly to drug-dependent antibodies that can only be detected in the presence of drug. The drug affects the immune system, causing production of red blood cell (RBC) autoantibodies; the clinical and laboratory findings are identical to autoimmune hemolytic anemia (AIHA), other than the remission associated with discontinuing the drug. Some of the mechanisms involved in DIIHA are controversial. The most acceptable one involves drugs like penicillin that covalently binds to proteins (e.g., RBC membrane proteins); RBCs become coated with drug in vivo and, a drug antibody (usually IgG) attaches to the drug-coated RBCs that are subsequently cleared by macrophages. The most controversial is the so-called immune complex mechanism, which has been revised to suggest that most drugs are capable of binding to RBC membrane proteins, but not covalently like penicillins. The combined membrane plus drug can create an immunogen; the antibodies formed can be IgM or IgG and often activate complement, leading to acute intravascular lysis and sometimes renal failure; fatalities are more common in this group. It is still unknown why and how some drugs induce RBC autoantibodies, sometimes causing AIHA [124].

6.3. Type III reactions

Type III reactions (immune-complex reactions) involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation. An
example is serum sickness. Type III hypersensitivity is caused by circulating immunocomplexes and is typified by serum sickness (a drug reaction in which multimeric drug-antibody aggregates form in solution). Preformed immunocomplexes deposit in various vascular beds and cause injury at these sites. Multimeric antigen-antibody complexes are efficient activators of the complement cascade through its classical pathway. The vascular beds in which immunocomplexes are deposited are determined in part by the physical nature of the complexes (their aggregate size, charge, hydrophobicity, etc.), and the specificity of deposition at locations can be surprisingly precise in some diseases (Figure 3C). Typical sites of injury are kidney, skin, and mucous membranes. Type III hypersensitivity is common in systemic lupus erythematosus (SLE) and underlies most of the pathophysiology of this chronic autoimmune disease. Some inflammatory reactions may blend features of type II and III hypersensitivity with the formation of immunocomplexes in situ [125].

6.4. Type IV reactions

Type IV reactions (delayed hypersensitivity reactions and cell-mediated immunity) are mediated by T cells rather than by antibodies (Figure 3D). An example is contact dermatitis from poison ivy or nickel allergy, tuberculosis, leprosy and sarcoidosis. In tuberculosis, cellular hypersensitivity, the delayed type of allergy, may be defined as an immunological state in which lymphocytes and macrophages are directly or indirectly sensitive to tuberculin, activate macrophages [126], and can passively transfer delayed hypersensitivity to the normal host [127]. Lymphocytes, when exposed to tuberculin merely produce a toxic or irritating product affecting macrophages, whether they sensitize macrophages to tuberculin [128]. In tuberculosis, delayed hypersensitivity is both beneficial and detrimental. In low concentrations, tuberculin stimulates the development of immunity in macrophages. Therefore, the presence of hypersensitivity is an asset in preventing pulmonary tuberculosis for only small units of one to three bacilli that reach the alveolar spaces where the infections begins. In high concentrations, tuberculin kills macrophages and thus is responsible for the liquefaction of caseous foci. This process results in tremendous extracellular multiplication of tubercle bacilli followed by their spread throughout the bronchial tree and to the other people [129].

7. Pathogenesis of autoimmunity (loss of immunological tolerance)

7.1. Gene base of autoimmunity

Despite the various immunological mechanisms to maintain tolerance to itself, there are certain individuals who develop autoimmunity. In 1986, the idea was postulated that the T and B cells specific for antigens coming from infecting pathogens, also generate a cross reaction against autoantigens even though the pathogens are eliminated. This type of response is initiated by low affinity T cells that have escaped the central tolerance. In addition, there is a genetic component capable of initiating and causing a persistence of autoimmunity and, therefore, trigger an autoimmune disease. However, epigenetic factors also play an important role in their development. They have been classified as a specific organism or systemic, with
the genetic susceptibility in the alleles of class I and class II molecules, a large part of the cause of the occurrence of autoimmune diseases such as systemic lupus erythematosus and type I diabetes mellitus [90]. Thus, the appearance of polymorphisms in more than 50 genes, among which a small number has been identified that affect the expression of molecules involved in the general activation of T cells, causes a high susceptibility to type I diabetes. In the case of the presentation of systemic autoimmune diseases, genetic susceptibility occurs in the general activation of B lymphocytes, affecting the signaling and survival receptors, which allows the autoreactive B cells of higher affinity to escape from the negative selection. Also, the genetic deletion of certain TLRs, such as TLR-9, increases the susceptibility to manifest autoimmune diseases. Depositions of antigen-antibody complexes in tissues, such as kidney, have been an important factor in the manifestation of autoimmune diseases. This is due to the variation in certain genes such as those responsible for synthesizing the components of the complement and its receptors, which can initiate autoimmune pathologies. Another important factor that triggers autoimmunity is the loss of certain immunoregulatory mechanisms. Such is the case of a chronic stimulation of the TCR, by a persistent antigenic exposure that can deregulate the immune response through adaptive tolerance mechanisms. A loss of the energy of autoreactive T lymphocytes, a failure in cell death by apoptosis of autoreactive T cells, the loss of suppression of these cells due to T<sub>reg</sub> lymphocytes, polyclonal activation of autoreactive T lymphocytes, may also occur among other mechanisms that can trigger autoimmunity [130]. Finally, autoimmune diseases can affect a specific cell type, several cells or the entire organism. Its initiation will depend on the pathways by which the immunological tolerance is altered, being of great importance the genetic predisposition that certain individuals present.

7.2. Autoimmune diseases

Autoimmune diseases are a consequence of an immune reaction against an autoantigen. They can affect a single organ or cell type; however, they are usually also systemic, as is the case of the onset of rheumatoid arthritis or systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a rare disease with a prevalence of 3.3 to 8.8 per 100,000 children. There is a high frequency reported in Asians, African Americans, Hispanics and Native Americans; the age at which it usually manifests is between 11 and 12 years of age and about 80% of adults who have SLE are women [131]. It is a multisystemic autoimmune disorder characterized by extended immunological dysregulation, formation of autoantibodies and immune complexes, resulting in inflammation and potential damage to a wide variety of organs. The clinical manifestation presented is nonspecific, such as the appearance of fever, fatigue, anorexia, alopecia and arthralgias. Symptoms such as generalized inflammation, including lymphadenopathy and hepatosplenomegaly, may manifest during the onset of SLE. However, the hallmark of this disease is the appearance of a butterfly-shaped malar rash. This condition can affect any organ of the system and its diagnosis is given through clinical manifestations and laboratory tests. Such is the case of the search for antibodies such as antinuclear antibodies (ANA), which are present in the serum of almost 98% of patients with SLE; Anti-dsDNA antibodies are present between 61 and 93% of patients with active disease; Anti-Smith antibodies are highly specific, but they can be found only in almost 50% of patients; Antibodies such as anti-Ro, anti-La, anti-U1RNP, anti-histones and rheumatoid factor, can also be used as a diagnosis of SLE. The indicated treatment is according to the activity of the disease and its severity, as well as the organs affected by
the SLE. The immunopathogenesis of this disease is mediated by the recruitment of autoreactive T cells and excessive plasma levels of proinflammatory cytokines. In addition, dendritic cells and subpopulations of T cells such as Th1, Th17 and regulatory T cells are significantly altered in function and number. However, the fundamental immunological dysfunction in the appearance of SLE is the loss of tolerance to nuclear antigens. There are defects that promote the presentation of autoantigens and the response to apoptotic residues in an immunogenic form; also, those faults that affect the signaling of the T or B cells, which causes the autoreactive abnormal stimulation of the lymphocytes; as well as those defects that promote the survival of autoreactive lymphocytes. Therefore, the loss of immunological tolerance is a factor that causes the presentation of systemic lupus erythematosus [132].

Rheumatoid arthritis (RA) is a chronic inflammatory multisystem disease characterized by destructive synovitis, in which all joints can be affected, mainly the small joints of the hands and feet. RA is a chronic progressive disease that results in decreased functional capacity and quality of life. It can manifest in individuals with genetic predisposition; however, it is of unknown etiology. It affects 0.2 to 2% of the worldwide, in a population of 40 years old, although it could happen at any age [133]. The diagnosis of RA occurs through the presentation of clinical manifestations, such as the onset of arthritis of at least 3 joints and morning stiffness of more than 30 minutes, as well as an exacerbated joint inflammation with the presence of pain. Likewise, blood concentrations of C-reactive protein and rheumatoid factor are evaluated, which will be elevated depending on the inflammatory activity of the RA. Another determinant with a high probability for the diagnosis of the disease is the evaluation of anti-CCP antibodies. The immunopathogenesis of RA results from the loss of immunological tolerance, with the consequence of an elevated secretion of proinflammatory cytokines such as IL-6, which is found in some patients, in high quantities in synovial fluid. In addition, the formations of autoantibodies that attack the joints of the entire organism are among the main causes of the presentation of RA [134].

8. Conclusion

The immune system is characterized by a network of complex mechanisms whose main objective is to protect the body. However, if there is a failure in its regulation, it can generate hypersensitivity and/or autoimmunity. For this reason, it is very important to know how our immune system works and how these pathologies originate. Currently, anaphylactic shock and skin reactions are the most frequent hypersensitivity reactions affecting organs and tissues. There are several mechanisms and factors involved which triggers hypersensitivity reactions. On the other hand, although autoimmune diseases are relatively common and our current knowledge about the mechanisms involved in their pathogenesis is very limited.

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Conflict of interest

We have no conflict of interest related to this work.

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