The collection of essays reviews, explores, and reports state-of-the-art autoimmunity issues with a cause and effect relationship. It provides a comprehensive presentation of immunity and autoimmunity and their connection to related diseases, current trends, data and possible future developments in health sciences. As such, it represents a unique resource for medical educators, medical practitioners and academics.

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Human Autoimmunity and Associated Diseases

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Edited by
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PREFACE

The immune system is a complex system that forms the defense mechanism against diseases in a living thing, recognizes and destroys pathogens and tumor cells, and protects the body from foreign and harmful substances. Autoimmunity is the impairment of immunological tolerance and an immune response against one's own antigens. Autoimmunity is still not fully understood for its reasons and treatment possibilities. We examined the immune system and autoimmunity in terms of its causes, mechanism of occurrence and its relationship with various diseases and treatment approaches. New studies on immunity and autoimmunity are constantly being carried out, and new diagnostic and therapeutic protocols are emerging. For this reason, it is important to follow and compile current studies. This book will examine current, emerging, and cutting edge approaches to autoimmunity. This book discusses the issue of immunity and autoimmunity in different aspects such as epigenetics, genetics, pregnancy, microbiota, male and female infertility, anesthesia applications, HIV, covid-19, foods and more.

The Editors

CHAPTER ELEVEN

CHEMISTRY, BIOCHEMISTRY AND AUTOIMMUNITY

TANER DAŞTAN

Introduction

Many mechanisms, molecular and cellular events, and responses are interferenced under autoimmunity. The dynamic biological system formed by the realization of the laws of the sciences of chemistry and physics is constantly in motion in maintaining metabolic activities in the body, in the fight against foreign molecules, in the formation of the immune response, and in the realization of autoimmune reactions. The formation of the immune response in living systems, the synthesis and interactions of molecules that occur during the immune response, and even the molecules that cause the immune response are all regulated with biological reactions maintained by chemical mechanisms. There is a constant chemical activity in the form of molecule synthesis, and the defense and destruction of foreign molecules for the continuity of life in the organism. Some immune responses emerge immediately after encountering a foreign molecule or molecules. Polypeptides for which the immune system is normally self-tolerant can create autoimmune responses, if changed. Self-peptides can be changed with genetic and epigenetic mechanisms. An autoimmune reply can also result from native antibodies, changed peptides and self-antigens. Native autoantibodies can function as template molecules for the obtaining of pathogenic autoantibodies (Atassi and Casali 2008). Clinicians follow the increasing gamma globulin, the deposition of denatured gamma globulin, and the accumulation of lymphocytes and plasma cells to diagnose an autoimmune state (Lester and King 1963).

The innate immune system, being the first layer of an organism's immune system, is common to all multicellular organisms (Aristizábal and González 2013). Evolutionarily, the innate immune system has a preceding history compared to the acquired immunity in species (Janeway and

Medzhitov 2002). The innate immune system constitutes an organism's repertoire of non-specific and natural immune responses against foreign substances. Consequently, the innate immune system is the fast-acting, first-response mechanism of organisms that can produce responses in minutes to hours (Chaplin 2003). The innate immune system has a wide array of constituents that make up their generalized, all-purpose role in self-preservation and functioning. To date, the contents of the innate immune system comprise the following categories: cellular and anatomical physical barriers, cellular enzymes, phagocytes, antimicrobial peptides, signal receptors, effector cells, cellular receptors, and mediators (Beutler 2009; Kumagai and Akira 2010; Takeuchi and Akira 2010). The coordinated efforts of these components enable the innate immune system to prevent or eliminate foreign substance invasions and stimulate, in other words, turn on the acquired immunity of the organism (Aristizábal and González 2013).

The particular malfunctioning of the epidermis layer of the skin is associated with an aberrant immune response against foreign substances that gradually translates into persistent inflammation, which is the case in atopic dermatitis. In this condition, the predominant finding is abnormalities in skin barriers coupled with potent T-helper cell 2 activity, which lead to dysregulation in the functioning of epidermal receptors. Since multicellular organisms with a system structure for digestion have their own microbiota, the digestive system is one of the most prominent hotspots for innate immunity as can be conferred from the presence of gamma and delta T lymphocytes and B cell subpopulations in the mucosae of the digestive tract (Delves and Roitt 2000; Chaplin 2003).

Primarily, the innate immune response has its ability to separate structural patterns between pathogens and host cells through invariable pattern recognition receptors (PPRs) (Takeuchi and Akira 2010; Wilkins and Gale 2010), which conveys an unmemorable immune response against recognized patterns (Takeuchi and Akira 2010). Molecular studies confirmed that pattern recognition receptors are highly secure, evolutionarily conserved structures that are specialized in recognizing the invariable antigenic patterns presented by pathogens (PAMPs) along with damaging inflammatory molecular patterns (DAMPs) from host cells. To date it is known that PPRs include TLRs, NLRs, CLRs, and RLRs (Kumagai and Akira 2010; Hoffmann and Akira 2013). It is also necessary to note that peptidoglycan recognition proteins (PGLYRPs) are also crucial PPRs even though they are mostly excluded from classical categorizations. Nevertheless, microorganisms have their own means to deceive innate immunity. The complement system (CS) is one of the foremost mechanisms of the innate immune organization comprising of molecules that would

enhance the immune response against bacteria or foreign molecules and the CS has regulatory roles in adaptive immunity, homeostasis and autoimmunity (Parra-Medina et al. 2013).

Epidermal chemical barrier

Keratinocytes are known to constitute both a physical and chemical defense against mainly cutaneous microbial pathogens through their ability to secrete antimicrobial peptides (AMPs). While AMPs are known to initiate an immune response against cutaneous pathogens, there are studies implying their role in tissue healing. Among the known AMPs, LL-37, the beta-defensin family, RNases, S100 family proteins, dermcidin, and REG3a are recognized for their antimicrobial properties (Nakatsuji and Gallo 2012). Naturally, the most pronounced effects of these molecules are their antimicrobial activities, but they have secondary effects as well; for example, certain beta-defensins are produced resulting from the presence of inflammatory cytokines (Gehr et al. 1993; Goto et al. 2013), S100 family proteins have their expression increased in sebaceous glands (Gallo and Hooper 2012), dermcidin stimulates epidermal cytokines and chemokines (Rieg et al. 2004; Niyonsaba et al. 2009), and REG3a has a role in wound healing. Again, it is noteworthy to mention that the chemical barrier conferred by the skin is in direct relation with the physical prospect as seen in the breakdown of filaggrin into naturally moisturizing factors such as uronic acid. In the context of tissue healing in cases of wounding, REG3a is shown to enhance the healing process through the limited stimulation of keratinocyte proliferation. This contribution to wound healing is related to the involvement of PPRs, in the cases of wound formations, i.e., stimulating REG3a (Aristizábal and González 2013). Induction of PPRs in wound formations is shown to be in direct relation to the vitamin D levels, indicating the immunity enhancing property of vitamin D. While all known PPRs in the cytoplasm and cell surface include nucleated cells, there are minor groups of PPRs that are secreted and working as adaptors between cells (Aristizábal and González 2013).

Toll-like receptors (TLRs)

Currently, different TLRs are known both in the cytoplasm and cell surface levels (Shimada et al. 2012). All TLRs include a leucin-rich repeat (LRR) domain for ligand binding and pathogen recognition, and a toll/interleukin-receptor (TIR) domain enabling an adaptor function. There are different ligands for different TLRs and different adaptor molecules taking roles in

different signaling pathways. Overall, all adaptor molecules have their roles in transcriptional activation and inflammation regulation through cytokine and chemokine expression (Akira and Takeda 2004; Parihar et al. 2010).

C-type lectin receptors (CLRs)

As a major subgroup of PPRs, CLRs have the ability to distinguish sugar moieties found on bacteria and fungi and recognize molecules associated with cell death (Hoffmann and Akira 2013). CLRs are known to have two groups, the first being located on the cell surface and the second being secreted forms of soluble CLRs, mainly by immune cells. Membrane-bound groups of CLRs (Dectin 1-2, DC-SIGN, Galectin-3) have the ability to recognize polysaccharide patterns found in bacterial and fungal cells and may have functions as co-receptors for TLR 2 (Bourgeois and Kuchler 2012). The soluble CLRs include collectins and pentraxins that are evolutionarily conserved and have roles in opsonization and pro-inflammatory regulation (Blasius and Beutler 2010).

Nod-like receptors (NLRs)

The nucleotide-binding oligomerization domain (NOD) receptors (NLRs), being intracellular PPRs, have the ability to recognize cytoplasm-entering compounds from bacteria, including peptidoglycans (Kumagai and Akira 2010; Takeuchi and Akira 2010; Wilkins and Gale 2010), and they are known to have several families. NLRs take regulatory roles in immunity initiation against a diverse array of pathogens (Saïd-Sadier and Ojcius 2012), and contribute to the formation of inflammasomes (Hoffmann and Akira 2013). Defects in NLRs, notably in the NOD2 gene, are presented to be in association with increased risk of having Crohn's disease (Abraham and John 2010).

RIG-like receptors (RLRs)

Retinoic acid inducible gen-I (RIG)-like receptors (RLRs) are known to be responsible for the expression of antiviral cytokines through the recognition of penetrated dsRNA from viruses, which makes RLRs a prime player as intracellular PPRs in immunity against viral infections (Kumagai and Akira 2010; Takeuchi and Akira 2010; Wilkins and Gale 2010; Saïd-Sadier and Ojcius 2012).

Damage-associated molecular patterns (DAMPs)

One defining trait of the innate immune system is its ability to recognize the molecular and cellular damage of host cells through the presence of DAMPs that have the triggering ability of immune response stimulation. DAMPs mainly come from damaging factors and necrotic cells, initiating the formation of inflammasomes, which is the defining difference between DAMPs and PAMPs (Saïd-Sadier and Ojcius 2012; Hoffmann and Akira 2013). Studies indicated that the erroneous sensing of ligands by PPRs results in persistent inflammation which is the case in autoinflammatory diseases (Hoffmann and Akira 2013).

The complementary system components and autoimmunity

The CS contains more than 60 plasma and surface peptides, multiple activation products, regulators and inhibitors, proteases and effector molecule receptors. This system covers an array of initially inactive molecules that become activated in sequence; therefore, working in a cascade of molecular events, as each activated molecule becomes an effector for the next. The sequential and trigger-driven nature of this cascade makes the CS a tightly regulated and quite complex mechanism of immune response (Walport 2001; Zipfel and Skerka 2009; Parra-Medina et al. 2013). Molecules of the complement system constitute more than 15% of the entire globular faction of the plasma by being in quantities of more than 3 g for each liter of plasma. Complement proteins are named based on their discovery sequence and fragment lengths (Walport 2001). Complement molecules are the eyes and ears of the immune system as they diligently do surveillance duties; therefore, defects in these molecules would result in disease-associated states, as they are also responsible for maintaining the physiological stress of organisms (Ricklin et al. 2010). Complement proteins are known to be in communication with both immune and non-immune cells, and T and B lymphocytes (Carroll 2004; Van Lookeren Campagne et al. 2007; Parra-Medina et al. 2013).

Three different pathways are seen in the complement cascade and these are known as the classical, lectin, and alternate pathways. The pathway initiated depends on the external stimuli, but regardless of the pathway, the main cascade steps are the same: initiation, C3 convertase activation and amplification, C5 convertase activation, and membrane attack complex (MAC) formation. All the main steps of each pathway as well as the entirety of the complement system are in tight regulation (Zipfel and Skerka 2009).

It is also known that the effects from the coagulation system (Markiewski et al. 2007) can initiate the CS cascade. The classical pathway initiates through antigen binding into antibodies but it is known that apoptotic cells and C reactive proteins as well as foreign nucleic acids can also initiate the classical pathway (Wagner and Frank 2010; Karsten and Köhl 2012). The lectin pathway is slightly different from the classical pathway as it does not require antigen binding into antibodies, but it does require binding of C-type lectins, mannose-binding lectin (MBLs), or ficolins into carbohydrate or peptidoglycan rich moieties. Among these MBLs is a well-characterized receptor for collectins which has calcium-dependent lectin binding domains, and MBLs have garnered more attention due to their ability to recognize and bind into the common structural patterns presented by various pathogens (Thiel 2007; Dunkelberger and Song 2010; Kingery et al. 2012; Thurman and Rohrer 2013). An in-vitro mechanism of by-passing was shown as the direct activation of C3 by bound MBLs in the absence of C4 and C2 (Parra-Medina et al. 2013).

Immunological homeostasis and immunological balance are retained by the regulatory effects of CS regulation factors, which would result in pro-inflammatory tissue damage if deficits occur on these factors. The CS has a mode of regulation called passive control activation which is supervised by regulatory proteins in the serum and on the cell surface. These regulatory proteins of the CS are in continuous connection with the complement proteins and responsible for the expression of multiple inhibitory regulation proteins (Parra-Medina et al. 2013).

Specific CS receptors (CR) located on cell surfaces, which are responsible for controlling cellular activities, are known to recognize activated complement products. Among these receptors, CR1, -2, -3, and -4 are more widely known while there are other receptors with limited specificity. Recent knowledge states that CR1 is responsible for the elimination of complement-bound complexes from the bloodstream and for inducing phagocytosis (Krych-Goldberg and Atkinson 2001), CR2 directs the antigen to the lymphoid tissue for immunologic memory (Fang et al. 1998; Carroll 2004; Wagner and Frank 2010), CR3 directs antigens into the secondary lymphoid tissue for elimination (Parra-Medina et al. 2013), and CR4 is in macrophages for antigen direction to the secondary lymphoid tissue (Wagner and Frank 2010). Other receptors may have inhibitory or pro-inflammatory roles or act as decoys (Scola et al. 2009; Parra-Medina et al. 2013).

The CS is also known to have vital roles in B-cell differentiation stages in adaptive immunity (Carroll 2004). Overall, CR1 and C2 are more pronounced in affecting humoral adaptive immunity. Particularly, CR2 has

diverse effects on B cells through affecting clonal expression, memory generation, or antigen delivery (Carroll and Isenman 2012). C3 and C5 are known to have roles in B-cell trafficking and migrations (Dunkelberger and Song 2010). T cells are known to be activated by APCs in lymph nodes, dependent on the pathogen and modifying factors. The CS has a role in the modulation of T-cell activities either directly or indirectly through the modulation of antigen presenting cells (APCs) (Kemper and Atkinson 2007).

Intensive research efforts revealed strong associations between the occurrence of autoimmune diseases (ADs) and aberrations in the innate immune system, and among the components, the CS has been implied in associations to autoimmune diseases, particularly with SLE and others like rheumatoid arthritis (RA), Sjögren syndrome (SS), multiple sclerosis (MS), anti-phospholipid syndrome (APS), and vasculitis. SLE is summarily described as the organism's loss of tolerance against autoantigens caused by released nuclei and proteins from dead cells. Studies implied susceptibility to SLE through the complement, namely the classical pathway, alterations with elusive and unclear remarks about its mechanism. Different hypothetical explanations were made on the nature of how classical pathway aberrations might contribute to susceptibility to SLE. While neither of the hypotheses was more convincing than others, they are still reinforcing further studies in exploring the unclear mechanism. Overall, the proposed approaches included concepts of alterations in the removal of apoptotic cells, rising autoantigens due to inefficient elimination, a persistent increase in autoantibodies due to inefficient elimination, avoidance of cytokine inhibition, and alterations in the functioning of regulatory factors (Alegretti et al. 2012; Knight and Kaplan 2012; Sturfelt and Truedsson 2012). Also, the reason why SLE patients have hypocomplementemia was attributed to the possibilities of genetic alterations, increased protein intake, or protein sequestration (Parra-Medina et al. 2013). Animal experimentation conducted on mice has revealed a close relationship between the occurrence of APS with deficits on complement elements of C3, C5, C6, and C5aR (Java et al. 2013). For the RA, the CS acting in the synovial tissue was found to be contributing to the pathophysiology of the disease. Certain research attributed this contribution to the genetic variants on regulatory proteins, while some others made connections to increased amounts of apoptotic granulocytes that are being recognized by the CS that drives pro-inflammation (Sturfelt and Truedsson 2012). Other research indicated an association between lectin pathway alteration and increased severity in RA due to the excessive osteoclastogenesis, while also proposing the COMP-C3 complex as a feasible biomarker for RA susceptibility (Sturfelt and

Truedsson 2012). Even though limited in scope, various studies made remarks on aberrations or deficits seen on complement elements of C4BP, C5a, C5aR, and MAC that are associated with susceptibility to autoimmune diseases (Zadura et al. 2009; Yuan et al. 2012; Kallenberg and Heeringa 2013). As a result, the CS is an intriguing avenue for therapeutic research for developing treatment strategies or drugs to address associated diseases with CS aberrations. The CS also provides research points for addressing pathophysiology of not only autoimmune diseases but also of cancer, allergy, etc. Currently, there are drugs for the inhibition of C3 and C5 that are approved for clinical applications (Wagner and Frank 2010). External immunoglobulins were used in Kawasaki disease and SLE (Wagner and Frank 2010). To date, there are still ongoing research studies for developing effective drugs that would target different aspects or components in the CS (Parra-Medina et al. 2013).

Cytokines, chemokine molecules and growth factors in autoimmunity

Biosignaling ensures the complexity and communication of cells of multicellular organisms with an evolutionarily achieved synchronicity in response and balance in the entirety of an organism. This is also a reason behind the occurrence of systems in higher organisms. In the context of the hematoimmune system, this perfect orchestration of biosignaling is achieved by the presence of molecules as cytokines, chemokines and growth factors that also have roles in embryogenesis and regeneration (Morán et al. 2013). The fundamental classification of biosignaling through cytokine actions has categories based on involved elements, the first being archetypical signaling cytokines acting through classical receptors that include two broad families of type 1 helical cytokine families, that is signaling via class 1 cytokine receptors (CRF1 family) and type 2 cytokine families signaling via class 2 cytokine receptors. Common gamma and beta chain receptor families, the prolactin family, and the interleukin 2, 6, and 12 (IL-2, 6, 12) families belong to the type 1 helical cytokine families while the IL-10 and 19 families and type 1 and 2 cytokine families, and IFN families belong to the type 2 cytokine families (Morán et al. 2013).

The IL-1 family represents highly pleiotropic yet repetitious cytokines with a wide array of different physiological functions having 11 members (Nelson 2008; Gomperts et al. 2009; Lefrançais and Cayrol 2012; Ohno et al. 2012; Peters et al. 2012; Hoffman et al. 2013). The IL-1 family would be expressed in response to so many different attacks on the integrity of an organism starting from mere inflammations to extremes like advanced

glycosylated end-products (AGEs). Most commonly seen members of the IL-1 family have a supporting role in system-wide ubiquitous responses and pro-inflammatory processes. Members with pro-inflammatory effects in the IL-1 family have the ability to stimulate or trigger adaptive immunity responses in both acute and chronic inflammatory conditions. Aside from the IL-1 family, IL-6 and TNFs are also known to take part in the management of acute inflammatory stress caused by various conditions such as hypertension and a lowered pain threshold (Morán et al. 2013). Today, it is known that IL-16 has three isotypes formed from an alternative splicing mechanism that are producing biologically active molecules with different affinities to distinct complexes. It is known that these isotypes are tissue specific in their expression as isotype 1 is expressed in leucocytes; isotype 2 in neural tissue, and isotype 3 in hemopoietic tissue. Overall, all isotypes have immunomodulatory functions on T-helper cells and take part in negative signaling (Nelson 2008; Gomperts et al. 2009; Tang et al. 2012; Hoffman et al. 2013).

Receptor and non-receptor tyrosine kinase families make up the cytokines that signal through immunoglobulin superfamily cytokine receptors. TNF receptor signaling of TNF cytokines also includes non-TNF-ligands. Chemokine signaling through G-protein associated chemokine receptors includes different motifs of CC, CXC, XC, and CX3C, and non-chemokine ligand receptors signal through chemokine receptors, namely chemerin. With the exception of CX3CL1 and CXCL16, which are membrane bound, all chemokines are soluble proteins with alkaline properties that can bind heparin. Chemokines are known to come together to form multimeric structures and their classification is based on common motifs indicated by the relative positioning of amino terminal cysteine residues. All chemokines have roles in immune regulation and inflammation development. Some others without a definitive relationship with the established families are grouped under orphan and other cytokines that include the IL-17 family and other individual cytokine families. Growth factors and other glycoprotein hormones with definitive immunologic roles include insulin, TGF-Beta and the activin families (Morán et al. 2013).

Interferons (IFNs) are cytokines with predominant glycoprotein motifs that are known to have antiviral, anti-proliferative, regulatory and modulatory properties, which can become apparent in the blood circulation under clinical manifestations (Nelson 2008; Gomperts et al. 2009; Wegenka 2010; de Weerd and Nguyen 2012; Whitaker et al. 2012; Hoffman et al. 2013; Pan et al. 2013). IFNs have three different types. Both type 1 and 3 IFNs are known to manifest in response to viral infections and type 1 INFs are acid stable. Type 2 IFNs are not resistant to acidic exposure and go into

action against allergic responses and intracellular antigens. Due to their ability to bind into diverse receptors, INFs share very little homology in function. Type I IFN genes are primarily regulated by IFN regulatory factors. In mammals, 13 subtypes of type 1 IFN-alpha were identified whereas single forms of other type 1 IFNs (IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-δ, IFN-τ) have also been discovered. All discovered type 1 IFNs are monomeric in structure (Morán et al. 2013).

The immune response

The development of immunity is a delicate result of complex interactions between 3 principal elements of the immunity, namely the antigen-presenting cells (APCs), T cells, and B lymphocytes. Summarily, the antigen that the organism encounters must be broken down into peptides by APCs, and if the broken-down peptides constitute a recognizable element for the major histocompatibility complex (MHC) class II protein, then they will be presented to associated T cells; namely, CD4 T-helper cells that have specific receptors for antigenic peptide coupled with MHC complexes. Following this activation of CD4 T cells, clonal expression of B lymphocytes will be triggered and B cells will continue to assume the mantle of APCs. Overall, the organism achieves enormous amounts of antigen specified T and B cells within 7 to 10 days that are an absolute requirement for the successful elimination of the pathogens (Miescher et al. 2003).

Nevertheless, a diverse array of affecting factors is in play during the development of the immune response. Summarily, this diversity of affecting factors mainly depends on the nature of antigens, and it is how APCs treat encountered antigenic peptides. If the initial expression of IL-12 by APCs is limited through an unclear cellular mechanism, then instead of Th cell 1 activation, Th cell 2 activation would be favored through IL-4 expression, which will produce the Th2 immune response that translates into a non-complement way of immune response development. Immune response localization is another defining or limiting factor in which Th immunity would be favored as in the case for the intestinal tract, which houses the specie-specific microbiota that is favoring strictly regulated CD4 T lymphocytes with a very limited inflammation response. In this context, APCs from Peyer's plaques have the directing role from which Th immunity would be developed against antigenic peptides. Summarily, Peyer's plaque APCs will decide for Th 1 or Th 2 immunity to develop or for mucosal tolerance development through regulatory T cells. Aside from APCs,

mucosae specific IgA would dictate the elimination of pathogens without a severe inflammatory response (Miescher et al. 2003).

The dynamic biological system formed by the realization of the laws of chemistry and physics, controlling Th activation reveals important aspects for immunopathology, which would have vital information on the direction of treatments. Th1 immunity has further complexity due to it being regulated by both afferent and efferent pathways which is the case in the cellular immune response. However, it should be noted that the cellular immune response is mainly cytotoxic and initiated through MHC class I complexes without the need for CD4 activation, which further complicates the clear distinction between Th 1 and 2 immunity development. This situation is also the case in autoimmunity development as while some autoimmune diseases exhibit dependence on MHC class II complexes, some others exhibit dependence on MHC class I complexes, which differentiates the involvement of whichever Th activation would be accounted for (Miescher et al. 2003).

Mechanisms of cellular and tissue disorders in ADs

In medical practice, practitioners have a tendency to consider antibody related conditions in the limited scope of B-cell pathologies. However, it is now known that B-cell expression has in fact a dependency on T-cell activation, which has revealed new avenues for understanding the antibody related conditions. It should be noted that B cells would provide antibodies whatever T cells are directing them to, including the organism's own constituents. Therefore, what essentially protects the organism against the B-cell menace is actually T-cell dependency. Antibody mediated conditions can arise from antibodies acting directly or indirectly on targets through cytotoxic or structural effects. This demonstrates that what begins with a seemingly unapparent clinical condition slowly develops into serious clinical manifestations through autoreactive T-cell driven B-cell expression. Various research studies were conducted on different diseases to reveal and define the active role of antibodies in the development and severity of ADs (Miescher et al. 2003). The classical diagnostic approach to autoimmunity involves serological parameters, which bias the practitioners to relate autoimmunity to rather misleading results from serology. However, not all autoimmune disorders, particularly collagen diseases, have clear indications present in serology, which seriously hampers the diagnostic power on truly obtaining precise results from such patients. Over time, the histopathology research conducted on various diseases such as collagen-induced arthritis and other autoimmune tissue inflammations has revealed clear associations

with cellular immunopathology that is directed through macrophages, T cells, and B cells. Following the identification of differences between Th 1 and Th 2 in cellular immunity, new research avenues have become apparent for elucidating which Th immunity is developing and responsible in which autoimmune conditions for designing target-specific therapeutic strategies. For a striking example in this aspect, research revealed Th 1 immunity in RA which is producing excessive amounts of TNF to manifest severe inflammation and tissue damage. Overall, there is a significant need for specified diagnostic approaches to determine self-reactive T cells, and to determine which Th immunity is active in the patient (Miescher et al. 2003). The complement system is the multifaceted weapon with a diversity of action of the innate immune system, which indicates the delicacy of the immune system with its tightly controlled cascaded nature and the different elements in either the serum or on the membranes. Overall, it is now known that the CS has a wide array of functions in the immune system but the most critical functions can be summarized as chemotaxis, phagocytosis, leucocyte and B-cell activation, and the elimination of immune complexes and apoptotic cells (Miescher et al. 2003).

Conclusion

The immune system is a defense system that protects organisms against all kinds of infections and a defense system that protects against any foreign substance. It consists of immune system cells (T and B lymphocytes, leukocytes, natural killer cells, monocytes, eosinophils, basophils) and some molecules (such as immunoglobulins, complements). Immune system cells recognize their self-tissue and tolerate self. They receive this training while the bone marrow and the thymus are still being formed in the womb. Depending on a disorder (genetic or structural) that will occur at this stage; some of the immune system cells of the person do not recognize some structures of their own tissue and begin to consider them to be foreign. However, there are healthy normal cells that keep these autoreactive cells under control. Under the influence of environmental factors (infections, severe stress, smoking, microbiota, silicon exposure, etc.), control over autoreactive cells loosens and proliferates; and disease symptoms occur over time. Here is autoimmunity, where self-tolerance is lost; disease development due to this is called autoimmune disease. The activation of autoreactive molecules and their positive and negative immune responses are placed in each of these steps. During all these processes, many molecules are produced, many molecules interact with each other, and events are observed, such as the disruption of different pathways of the

organism, and the change and transformation of cellular activities. Each molecule that reacts during all these processes has a specific chemical structure, and every event that takes place inside the cell has a chemical mechanism. The genetic infrastructures and various environmental factors induce such positive or negative immune responses in ADs. It is thus necessary to understand in detail the autoimmune phenomena in each patient with their genetic, biochemical, physiological and even psychological states to edit a proper therapy that suppresses pathological autoimmune responses without disturbing normal immune system functions.

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