Chapter 1

Introductory Chapter: Immune System Dysfunction and Autoimmune Diseases

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1. Introduction

Currently, a major health concern is focused on many diseases caused by heterogeneous aberrations of the immune system, including autoimmune diseases, which account for one of the top leading causes of death worldwide. The molecular approach has provided an answer to several fundamental questions about the etiopathogenetic mechanisms of such diseases and has thus considerably provided the opportunity for researchers and clinicians to compare their own experiences and to bring their hypotheses closer together. It therefore appears appropriate to propose this collective work, which contains various and often specific subjects on autoimmune disorders.

2. Immune system: self- and non–self-discrimination

The essential functions of the immune system is to maintain the coherence of the cells and tissues and to ensure their integrity by rejecting foreign aggressive substances or infectious agents, that is, the "nonself," and the immunogenic altered self, referred to as "modified self," while respecting the normal components of the host, that is, the "unmodified self-antigens" [1, 2] (**Figure 1**).

Two strategies are adopted to preserve immune system integrity and coherence [3]: the first strategy corresponds to the innate immunity, also known as nonadaptive immunity, which is triggered immediately after infiltration of microorganisms or upon danger signal integration; the second one involves adaptive immunity, which the activation takes place after pretreatment of the antigen by innate immune cells. Adaptive immunity develops more slowly than innate immunity. It is characterized by immunological memory, allowing it to generate faster and more intense responses in subsequent exposures to the same antigen, which has previously induced a primary immune response.

Cells of innate immunity can recognize, through membrane or intracellular genetically encoded receptors (pattern recognition receptors, PRRs), invariant motifs (pathogen-associated molecular patterns, PAMPs) that are displayed on a large number of pathogens, but absent in host cells. These receptors are preformed or very rapidly inducible in humans. They

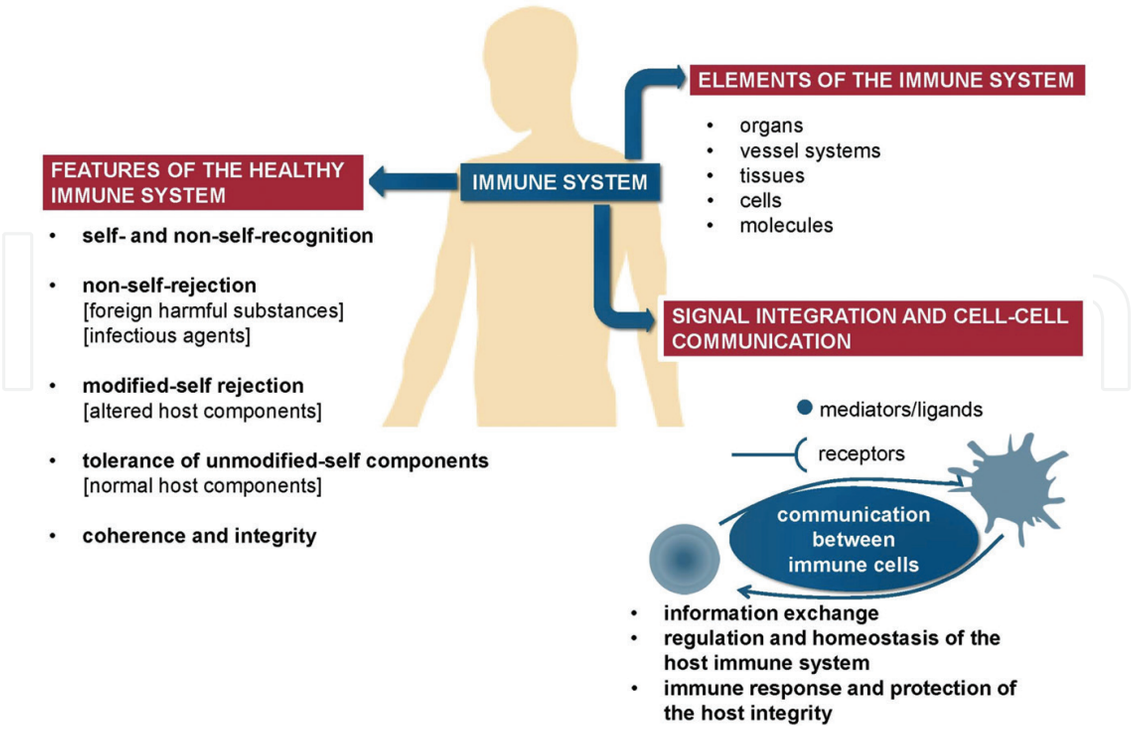

Figure 1. Overview of the immune system. The immune system contains a complex collection of organs, tissues and vessel systems between which circulate constantly immunocompetent cells of innate and adaptive immunity. These cells communicate with each other via receptors that integrate external signals in the form of soluble mediators or insoluble extracellular ligands or counterreceptors. The binding of a signal induces a transformation of the external information into internal information, a process referred to as a signal transduction inside the cell, and a modification of the properties of the molecular targets involved in a cell signaling pathway. The interaction between different cell types promotes full harmony of their various and vital functions: regulation, homeostasis, immune response, and protection of the host integrity. The alteration of any of these functions causes serious pathological disorders, including autoimmune diseases, cancers, immune deficiencies, and allergic diseases. Finally, a healthy immune system could be described by five main features: (i) self- and non–self-recognition, (ii) non–self-rejection, (iii) modified-self rejection, (iv) tolerance of unmodified self-components, and (v) coherence and integrity.

can also recognize and bind substances released from damaged host tissues and cells (damage-associated molecular patterns, DAMPs) [4].

The cells of the adaptive immune system—B cells and T cells—are derived from the same pluripotent hematopoietic stem cells [5]. These cells carry on their surface highly diversified antigen-specific receptors, which are able of interacting with a quasi-unlimited number of antigens, thanks to their structure diversity. B cells specifically recognize and bind intact antigens, through highly variable domains of their cell-surface receptors (B cell receptors, BCR), whereas T cells specifically recognize and interact via the highly variable domains of their receptors (T cell receptors, TCR) with peptide fragments derived from antigens in association with major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs) [6]. Two classes of such cells have been defined by their functions and their differentiation markers (cluster of differentiation, CD), but also by the class of MHC molecules they recognize: $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells that interact with peptide-class-II-MHC and peptide-class-I-MHC complexes, respectively [5]. The subset of $CD4^+$ T cells that express high levels of CD25 ($CD4^+$ $CD25^{high}$), so-called regulatory T cells (Tregs), is essential in maintaining immunological self-tolerance and prevention of autoimmunity. A deleterious autoimmune reaction

may be generated as a result of decreased frequency and/or function of Treg cells in both organ-specific and systemic autoimmune diseases [7]. Of note, regulatory cells are not limited to $CD4^+$ T cells but can include various immune cell subsets, such as $CD8^+$ Treg, Tr1 regulatory cells, Th3 cells, natural killer like T (NKT) cells, and Breg cells [8–10] that can prevent destructive immune responses and autoimmunity. Additionally, to establish a self-tolerance by the immune system, potentially dangerous autoreactive T cell and B cell clones must be deleted through negative selection or clonal deletion within mechanisms of central tolerance occurred in the thymus and bone marrow, respectively, before they develop into fully immunocompetent cells [11, 12]. Failure or breakdown of negative selection, which can also occur in the periphery, can lead to the development of autoimmunity and autoimmune diseases [11–15].

3. Reactions against self-antigens and autoimmunity

When the immune system is abnormally overactivated, as a result of defective regulation function, and triggers a strong reaction against its unmodified components, autoimmune pathological manifestations might develop. Autoimmune responses involve, as a classical immune response, T cells, B cells, APCs, inflammatory cells, antibodies, and many other mediators of immunity such as cytokines.

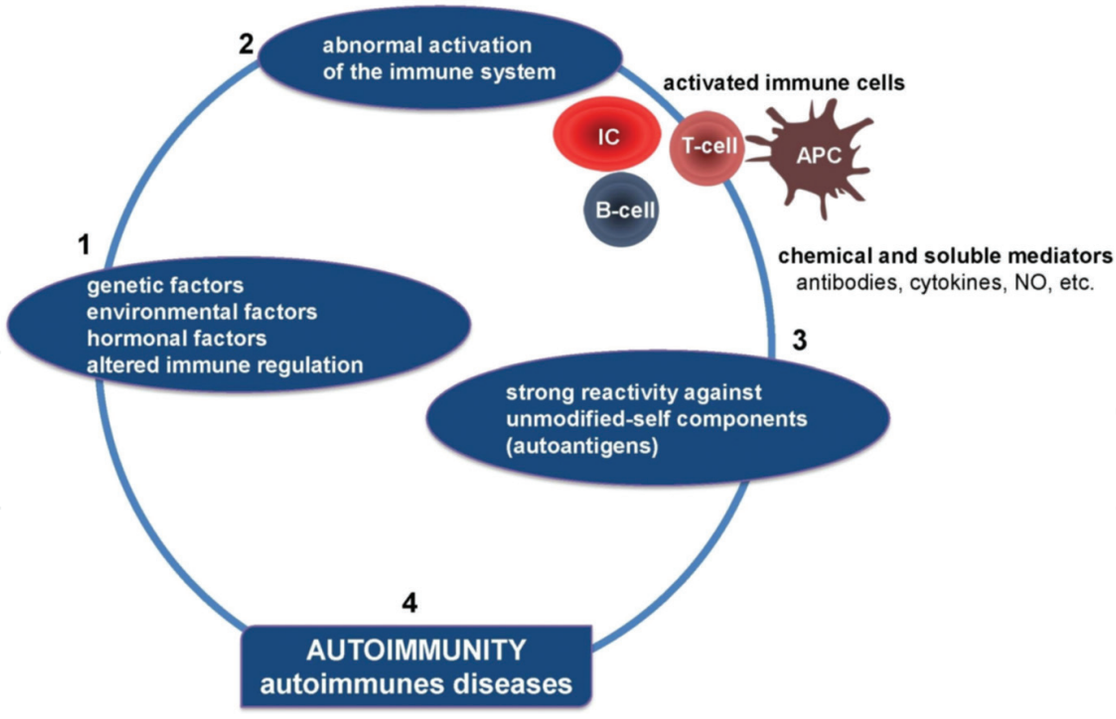

Figure 2. Pathophysiological mechanisms of autoimmune diseases. Autoimmune diseases are multifactorial diseases, and their etiologies are not yet fully known. Their development depends on genetic susceptibility, environmental factors, hormonal factors, and immune dysregulation. These factors may influence, according to different mechanisms, the abnormal activation of potentially dangerous autoreactive cells. Other components are involved in enhancing the autoimmune process, including, antigen-presenting cells, inflammatory cells, and many chemical and soluble mediators such as vasoactive amines, nitric oxide, lipid mediators, growth factors, complement system, cytokines, etc. APC, antigen-presenting cell; IC, inflammatory cell; NO, nitric oxide.

Numerous factors have been associated to pathological autoimmunity, including genetic predisposition and epigenetic change, environmental factors (nutrition, viral and bacterial infection, and ultraviolet radiation), drugs (beta-blockers, antipsychotics, and antibiotics), vaccination, sex hormone, etc. [16–22] (**Figure 2**).

4. Autoimmune diseases

Autoimmune diseases and autoimmune-related diseases are numerous (there are more than 130, AARDA). Some of them are more severe or more frequent than others. They are conventionally distinguished in organ-specific autoimmune diseases, in which the autoantigen target is localized in one organ or tissue, and systemic or nonorgan specific autoimmune diseases in which autoantigens are widely distributed in the body or spread throughout several organs (**Figure 3**). In addition, common autoimmune disorders can coexist in the same patient [27, 28], which further complicates diagnosis and medical management.

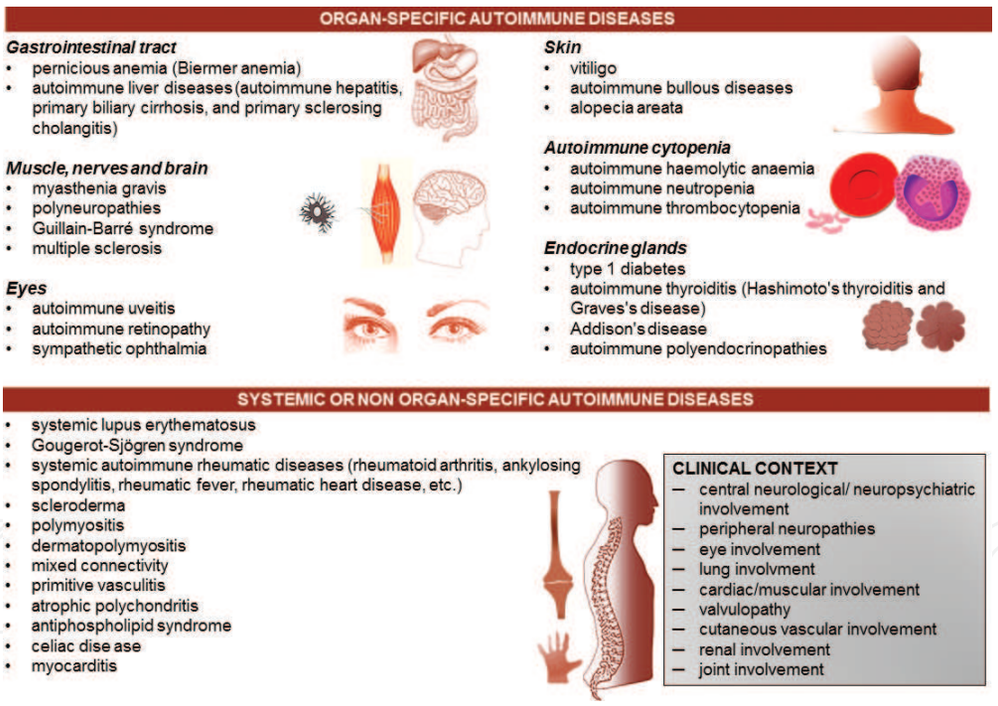

Figure 3. Types of autoimmune diseases. There are two categories of autoimmune diseases: organ-specific autoimmune diseases and nonorgan specific autoimmune diseases, also called systemic diseases. Organ-specific autoimmune diseases are restricted to certain organs or a particular tissue. Nonorgan specific autoimmune diseases are characterized by extensive lesions that are secondary to an autoimmune reaction against ubiquitous autoantigens. There are also many overlap syndromes that may be characterized by the association of two or more organ-specific and systemic autoimmune diseases, due probably to the existence of common immunogenetic factors. Finally, such categorization of autoimmune diseases does not take into account diseases resulting from immune reactions against foreign antigens expressed in a target tissue, especially in viral diseases. It also ignores autoimmunity observed under physiological conditions in the absence of any pathological tissue damage [23–26]. (The list of pathologies presented in this figure is not exhaustive.).

Although it is not easy to determine for each individual the exact cause of pathological autoimmunity, given the extensive heterogeneity of autoimmune disorders [29], relevant research strategies with advanced technologies are developed or are still under investigation to control or prevent these diseases in a wider context (**Figure 4**).

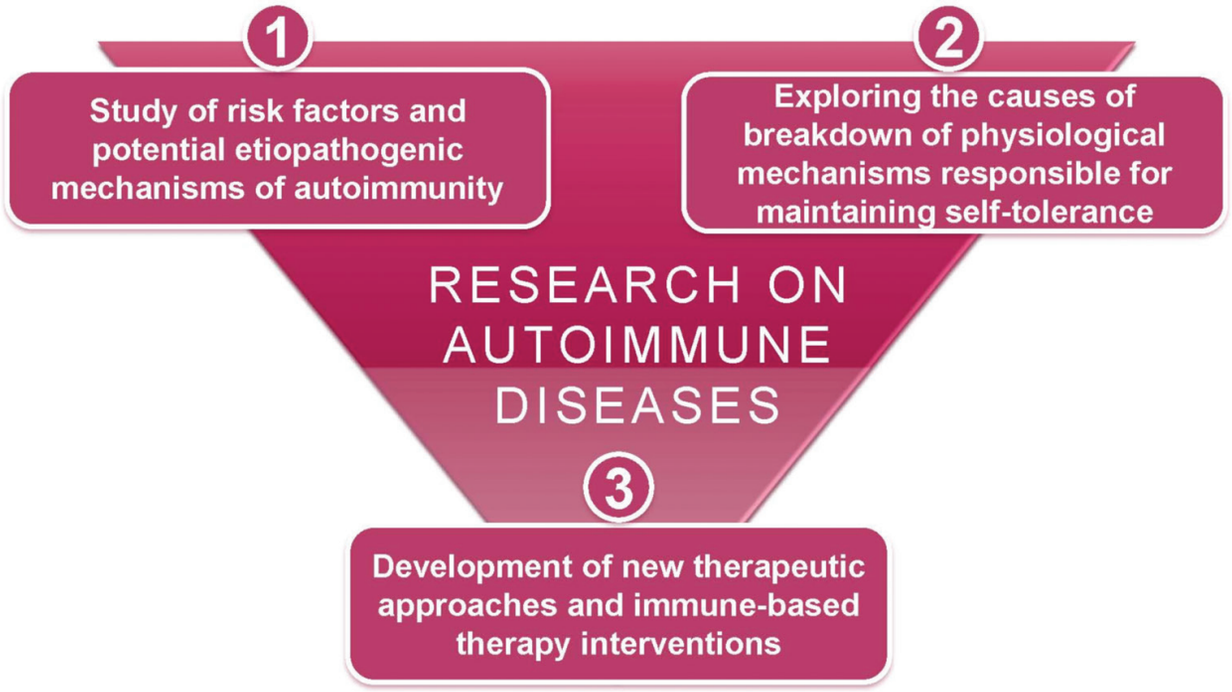

Figure 4. Strategies for exploring autoimmune diseases. The exact causes of autoimmune diseases are not yet fully understood, but are the subject of intensive researches that are focused mainly on three main axes: (i) study of the risk factors and potential etiopathogenetic mechanisms underlying these illnesses, (ii) research on the causes of the breakdown of the mechanisms responsible for maintaining tolerance to self-antigens, and (iii) development of innovative therapies and immune interventions. Current treatments aim to suppress autoimmune response and inflammation and alleviate the functional consequences of cellular or tissue damage.

5. Conclusions

The essential function of the immune system is the eradication of aggressive elements, particularly infectious agents and tumor cells. In order to ensure normal immune functions, lymphocyte clones which are capable of strongly recognizing harmless or unmodified elements of the self are eliminated or suppressed so that under normal conditions no autoimmune reaction is observed.

The explosion of knowledge thanks to molecular biology over the past few decades has opened new perspectives in the search for risk factors that could be directly involved in the occurrence of autoimmune diseases. It is now well-established that these diseases may be caused by a combination of a genetic predisposition and a triggering factor.

More than 130 autoimmune diseases and autoimmune-related diseases have been identified. Most often, a distinction is made between organ-specific autoimmune diseases, for which

specific organs are the target of an attack by the immune system, and nonorgan specific autoimmune diseases which are of a systemic manifestation.

Significant progress has been made in understanding the etiopathogenetic mechanisms of autoimmune diseases. They should undoubtedly lead to more effective therapeutic strategies. Currently, there are multiple potential treatments that often rely on immunosuppression. Nevertheless, the best strategy would be to act more selectively on the self-reactive cells that are abnormally overactives.

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