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Review

Autoimmunity and immune tolerance: A review

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ABSTRACT

The normal immune system has the capacity to react with different microbes. The immune system has the responsibility for identifying and executing proper responses to eliminate non-self-antigens and prevent the harmful response to self-antigens, which is known as immune tolerance. Immune tolerance refers to the unresponsiveness of the immune system toward certain substances or tissues that are normally capable of stimulating an immune response. It is important for normal immune balance, and failure or breakdown of that tolerance results in autoimmunity. Immune tolerance can be categorized into two, central and peripheral tolerance depending on the site it is initially enhanced. Peripheral tolerance can be carried out by different mechanisms such as induction of anergy, deletion, ignorance and regulatory T cells and others. Autoimmune disease is a condition that is triggered by the immune system inducing an attack on self-molecules due to the deterioration of immunologic tolerance to auto-reactive immune cells and it is traditionally divided as organ-specific or systemic. These autoimmune diseases are correlated with factors including genetic factors, sexual hormones, environmental factors, chemical agents and other factors to the animal. The autoimmune diseases can be prevented by the action of regulatory T cells and also treated by B cell-targeted therapy and Rituxan anti-CD20-mediated B cell depletion.

Keywords: Autoimmune diseases, autoimmunity, central and peripheral tolerance, self-tolerance.

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ABBREVIATIONS: AAS, Antiphospholipidal antibody syndrome; **ADCC,** antibody-dependent cell-mediated cytotoxicity; **ADs,** autoimmune diseases; **APC,** antigen presenting cells; **CDC,** complement-dependent cytotoxicity; **CLE,** cutaneous lupus erythematosus; **CLL,** chronic lymphocytic leukemia; **CTL,** cytotoxic t lymphocyte; **dsDNA,** double stranded deoxyribonucleic acid; **HLA,** human leukocyte antigen; **MHC,** major histocompatibility complex; **MS,** multiple sclerosis; **PBC,** primary biliary cholangitis; **RA,** rheumatoid arthritis; **SLE,** systemic lupus erythematosus; **TCR,** T cell receptor; **Th,** T-helper; **Tregs,** regulatory T cells; **VCAM,** vascular cell adhesion molecule.

INTRODUCTION

The most remarkable characteristic of the normal immune system is its ability to react with an enormous variety of microbes. However, despite the fact that even lymphocytes with the ability to recognize self-antigens are constantly being generated during the normal process of lymphocyte maturation, usually the immune system does not activate them. This unresponsiveness is due to a series of mechanisms that prevent immune responses against self antigens, and thereby enable the immune system to discriminate between self and non-self antigens. Therefore, when these mechanisms fail, the immune system may attack the individual's own cells and tissues (Romagnani, 2006).

The immune system is a collection of biological processes designed to defend the body against invasion by infectious pathogens and tumor cells and this system involves innate, adaptive and memory responses that are constantly activated, adapted and improved to meet the challenge of evading pathogens. The immune system must be tolerant and distinguish between self and non-self, so that substances that are identified as non-self stimulate an immune response, while no harm is inflicted upon self (Takahashi et al., 2019).

The immune system is responsible for detecting and implementing proper reactions in order to remove non-self antigens and prevent the harmful response to self-

antigens, referred to as immune tolerance. To maintain immune homeostasis in balance, the individual must be tolerant of their own potentially antigenic substances. Once self-tolerance is disrupted, autoimmunity will arise (Jerne, 2004). Autoimmunity is a consequence of the breakdown of self-tolerance; the result is an attack of the immune system on different tissues and organs as if they were foreign invaders (Takahashi et al., 2019).

Immune tolerance is referred to as the state of unresponsiveness to molecules that have the potential to induce an immune response and ensures that the immune system does not mount a response against self-antigens. Failure of tolerance contributes to the induction of autoimmunity (Hocking and Buckner, 2022). Immune tolerance is essential for the maintenance of homeostasis. In the network of immune regulation, continuous stimuli-response interactions are in harmony with functional tolerance mechanisms (Takahashi et al., 2019).

The numerous antigens encountered by the host in daily life, especially through mucosal surfaces, challenge the highly reactive immune system, but the stimuli normally lead to healthy unresponsiveness, which means tolerance. Such unresponsiveness is essential for the well-being of the host (Kucuksezer et al., 2013). When the immune system is unable to differentiate between healthy tissues and potentially dangerous antigens, it results in autoimmune diseases (Cuthrell et al., 2022).

Autoimmune diseases (ADs) are the third leading cause of morbidity and mortality, after heart disease and cancer, in the developed world. Autoimmune diseases are devastating conditions in which the immune system is directed against the host, leading to the life-threatening destruction of organs (Takahashi et al., 2019). For autoimmune disorders to develop, a combination of genetic, immunologic, hormonal and environmental factors is required. The idea of molecular mimicry can be used to explain the immune system attacking its own host. The immune system typically fights antigens and develops a reaction in response to the antigens. In autoimmune illnesses, the immune system is unable to tell its own host cells apart from foreign antigens. Different autoimmune diseases appear in various ways, and their onset ages vary. Autoimmune disorders have a complicated origin, with genetic, hormonal, and environmental factors all contributing. Autoimmune diseases significantly affect pathophysiological processes. The complexities of the immune system have the primary purpose of defending hosts against infectious pathogens (Cuthrell et al., 2022).

Clearly, a healthy immune system must be capable of mounting a response against pathogens that invade the host. However, it is also important to maintain self-tolerance; that is, the immune system should not attack the body's own tissues (Alexander and Wahl, 2011). Depending on these facts, this work reviews autoimmunity and immune tolerance and the factors associated with them.

AUTOIMMUNITY AND IMMUNE TOLERANCE

Autoimmunity

Self versus non-self discrimination is a crucial feature of the immune system. Normally, the immune system can mount responses against foreign pathogens, but avoid attacking the organism's own tissues. Occasionally, however, self-tolerance mechanisms fail and the outcome is autoimmunity (Alexander and Wahl, 2011). Autoimmunity results when the peripheral mechanisms fail. The past few years have witnessed significant progress toward understanding the processes involved in autoimmune disease pathogenesis and the tolerance of T-cell breakdown. These advances involve the identification and characterization of the key cell types and surface receptors involved in the induction and prevention of autoimmunity. A great deal of information about CD41 effector T cells has been learned from these studies including the role of T-helper 1 (Th1), Th2, and Th17 sub-populations during normal immune responses and autoimmunity. These cells play a pivotal role in directing other inflammatory cells and driving differentiation by creating micro-environments filled with inflammatory cytokines and chemokines (Salomon and Bluestone, 2001).

Autoimmunity refers to the presence of antibodies or T lymphocytes that react with self-antigens and does not inevitably indicate that the self-reactivity has pathogenic significance. Autoimmunity is generally defined as a phenomenon in which antibodies or T cells react with autoantigens. Autoimmunity is present in all individuals and increases with age (Kazuhiko, 2004; Diamond and Lipsky, 2023).

Immune tolerance

Immune tolerance refers to the unresponsiveness of the immune system toward certain substances or tissues that are normally capable of stimulating an immune response. Self-tolerance is essential for normal immune balance, and failure or breakdown of that tolerance results in autoimmunity and autoimmune diseases infertility (Carvalheiras et al., 2012). Immunological tolerance is defined as a state in which the immune system does not positively respond to autoantigens (Kazuhiko, 2004).

Immunological self-tolerance comprises all phenomena that prevent the immune system from turning against self. Self-tolerance thus simply denotes the absence of autoimmunity. This state could be achieved in principle via passive mechanisms, for example, the absence of

activation of self-reactive lymphocytes or via active mechanisms that eliminate or functionally inactivate self-reactive lymphocytes (Klein and Kyewski, 2000). Tolerance is achieved through both central and peripheral tolerance mechanisms (Hocking and Buckner, 2022).

Central tolerance

Central tolerance refers to the elimination of auto-reactive lymphocyte clones before they become fully immune-competent, of which the main mechanism is negative selection. This procedure occurs in the stage of lymphocyte development in the thymus and bone marrow for T and B lymphocytes, respectively (Zhang and Lu, 2018). Central tolerance occurs in the thymus for T lymphocytes and the bone marrow for B lymphocytes and acts primarily through negative selection by eliminating immature T and B lymphocytes that recognize self-antigens (Hocking and Buckner, 2022).

Antigen-specific central tolerance of T cells requires a given self-antigen to be either expressed in the thymus or to enter the thymus via the blood or lymph circulation (Klein *et al.,* 1998). Since T cells do not recognize intact proteins, but proteolytically cleaved fragments thereof (peptide epitopes) bound to major histocompatibility complex (MHC) molecules, the efficiency of antigen processing and presentation is a limiting factor in the generation of a critical density of self-epitope/MHC ligands on thymic antigen-presenting cells (APC). It should be remembered that MHC class I antigens are expressed on nearly all somatic cells, while expression of MHC class II is restricted to a subset of hemopoietic cells, so-called “professional” APC and thymic epithelial cells. Remarkably, the minimal number of self-peptide/MHC class II ligands on the surface of an APC sufficient to induce negative selection has been estimated to be as low as 10 out of a total of 1 to 5 × 10^5 per cell (Peterson et al., 1999).

Peripheral tolerance

Peripheral tolerance takes place after the T and B lymphocytes leave the primary lymphoid organs (Hocking and Buckner, 2022). Due to the low frequency of a given antigen-specificity among the polyclonal T cell repertoire (estimates range from 1 in 10^4 to 1 in 10^6), physically tracking the fate of self-specific T cells has only become possible with the advent of T cell receptor (TCR) transgenic mice. These mice express a given transgenic TCR specificity on the majority of their T cells, thus allowing an assessment of the mechanism of tolerance induction. A number of elegant model systems have been devised making use of mice that co-express a transgenic, tissue-specific (neo) antigen and the respective transgenic TCR specific for this antigen. Many studies led to the common notion that the exit of potentially self-reactive T cells from the thymus does not necessarily lead to autoimmunity. Rather, several mutually non-exclusive peripheral mechanisms seem to secure tolerance of auto-specific T cells (Klein and Kyewski, 2000).

After T and B lymphocytes enter the peripheral tissues and lymph nodes, peripheral tolerance will occur to inhibit immune responses against the body's own tissues, which occurs primarily in the secondary lymphoid organs, such as spleens and lymph nodes. Mechanisms of peripheral tolerance include anergy (functional unresponsiveness), deletion (apoptotic cell death) and suppression by regulatory T cells. Autoimmune diseases may develop when self-reactive lymphocytes escape from tolerance and are thereby activated. However, the underlying exact mechanisms are not entirely known. Current knowledge suggests that autoimmunity stems from a combination of genetic variants and various acquired environmental triggers (Zhang and Lu, 2018).

The antigenic signal in the absence of a co-stimulatory signal would be tolerogenic for T cells. Accordingly, auto-reactive T cells specific for antigens uniquely expressed on tissue cells that do not express co-stimulatory molecules would be removed from the T cell repertoire. This mechanism of peripheral tolerance would provide a second safeguard by which auto-reactive T cells that could be activated by cross-reactive pathogens would be specifically eliminated. An essential component of an autoimmune response is local inflammation that favors mononuclear cell infiltration in a tissue probably as a result of induced expression of adhesion molecules such as vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM) -1, -2 by the vascular endothelium and the up-regulation of expression of MHC antigens by tissue cells (von Herrath et al., 1995) (Figure 1).

In the thymus, both high-affinity T and B cells undergo apoptosis. Low- and non-affinity T and B cells enter peripheral tissues and lymph nodes, where non-affinity T and B cells mature into immune cells and low-affinity T and B cells are deleted by many mechanisms, such as anergy, ignorance, deviation and homeostatic control (Zhang and Lu, 2018) (Figure 2).

Immune cells generate and experience central and peripheral tolerance. Tolerance fails because of the interaction of the wrong environment with the wrong gene, resulting in autoimmune disease (Zhang and Lu, 2018).

MECHANISMS OF IMMUNE TOLERANCE

Deletion

Immature B cells are destroyed through a process known

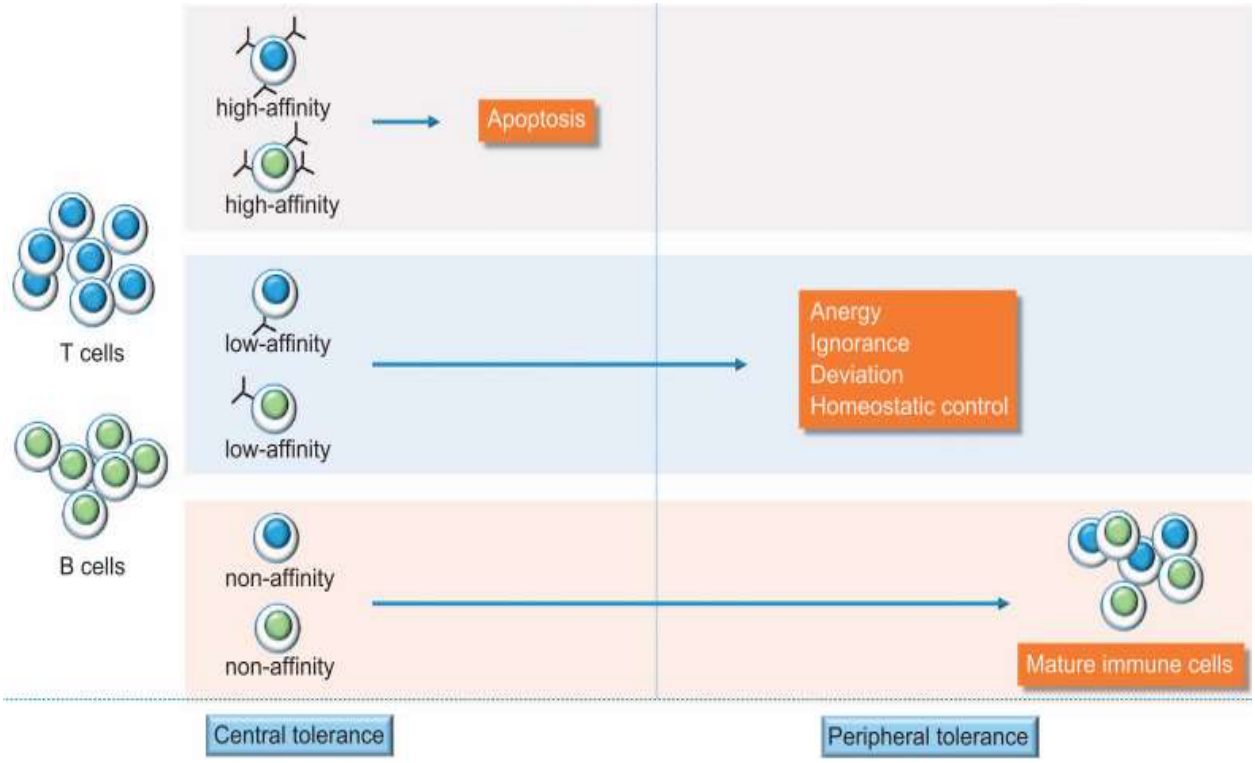

Figure 1. Central and peripheral tolerance.

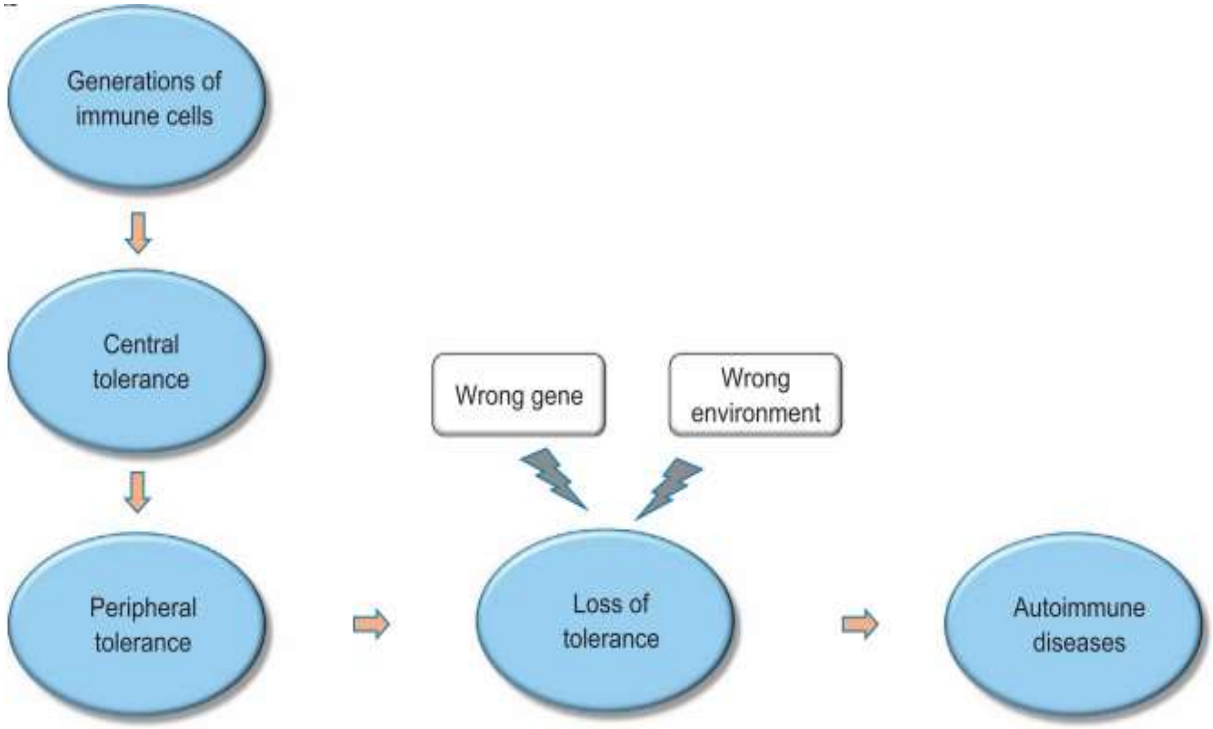

Figure 2. The process of loss of tolerance to autoimmune diseases.

as clonal deletion or clonal anergy if they express surface IgM that distinguishes common self-cell-surface antigens (Cuthrell et al., 2022). The conventional clonal deletion theory assumes that the immune system distinguishes between self and non-self and that auto-reactive B and T cell clones are eliminated before they mature (Kazuhiko, 2004).

In analogy to negative selection in the thymus, auto-reactive T cells may be eliminated upon encounter with self-antigen in the periphery. In initial experiments, the thymic checkpoint has been artificially bypassed by adoptively transferring naive, antigen-specific T cells into recipient animals that abundantly expressed the respective antigen. These T cells have proven to proliferate extensively in the absence of tissue damage prior to being eliminated by activation-induced cell death (Rocha and Von Boehmer, 1991), the latter being reminiscent of the down regulatory phase of a “classical” immune response. Recently, peripheral deletion was shown to be equally effective for antigens that are expressed in a more restricted, tissue-specific manner. In these cases, the target antigen is released from the tissue of origin and presented in a draining lymph node (Forster, 1998). Remarkably, this route of antigen presentation applies not only to MHC class II-restricted epitopes, which are as a rule derived from the extracellular space, but also to MHC class I-restricted epitopes. This latter pathway, heretical to the prevailing dogma of MHC class I antigen processing and presentation, is referred to as “cross-presentation” (Miller et al., 1998). It is still questionable whether deletion in the periphery actually represents a distinct “tolerance mechanism” that might even involve a specialized type of APC or reflects depletion due to chronic stimulation of specific T cells after differentiation into effectors in the lymph node without causing tissue damage. Such “exhaustive” stimulation has also been observed during the late phase of chronic infections (Moskophidis et al., 1993).

Induction of anergy

The two-signal model of T cell activation postulates that in addition to the TCR signal (signal 1) a second signal is required to fully activate naive T cells. The CD28 receptor and its ligand B7 have been identified as the first set of molecules capable of delivering signal 2, although recently additional receptor/ligand pairs including soluble cytokines have been described. Importantly, triggering the TCR in the absence of co-stimulation (signal 2) in vitro is not a null event but rather results in the functional inactivation of T cells. This condition has been termed “T cell anergy” (Schwartz, 1990).

Maintenance of self-tolerance via induction of anergy upon antigen encounter in peripheral tissues entails a paradox: Naive T cells are endowed with a specific pattern of homing molecules and recirculate between blood and lymph, but are thought to be incapable of accessing most peripheral tissues (example: the skin, muscle, or brain). The concept of tolerance via induction of anergy, however, postulates the encounter of self-antigens on non-lymphoid tissues as a mandatory step. A recent study revealing a time window in the early postnatal phase during which naive T cells may actually be able to patrol through peripheral tissues and encounter tissue antigens has shed new light on this conundrum (Alferink et al., 1998). Since thymic T cell output has been documented beyond such a critical time window, this concept in addition implies a “dominant,” regulatory component. In order to preserve lifelong self-tolerance, neonatally anergized T cells would thus have to imprint their tolerant phenotype upon recent thymic emigrants that are barred from penetrating peripheral tissues during adulthood (Douarin et al., 1996).

The emergence of anergic T cells has also been observed after chronic antigenic stimulation. Activation-induced cell death can be incomplete, leaving behind a small population of T cells that do not proliferate upon appropriate stimulation (Rocha and Von Boehmer, 1991). These cells produce a unique pattern of cytokines, in particular interleukin-10, which may be immunosuppressive (Tanchot et al., 1998).

Taken together, these recent observations suggest that anergic cells, contrary to previous beliefs, do have functional competence. Accordingly, the concept of anergy is currently understood not as the persistence of completely paralyzed cells merely filling space, but as a shift from effector potential to regulatory function (Alferink et al., 1998). It should be added that the molecular definition of anergy lags far behind its functional characterization.

Ignorance

Ignorance is another mechanism of peripheral tolerance. Through a variety of techniques, autoreactive T-lymphocytes ignore self-antigen during this process. The inability of lymphocytes to access self-antigens may be the result of a physical barrier, such as the blood-brain barrier, which can also be since lymphocytes were not exposed to enough self- antigen to prompt an autoimmune reaction (Cuthrell et al., 2022).

This mode of tolerance describes the “harmless” coexistence of naive, auto-reactive T cells and their respective target antigen on peripheral tissues (Miller and Heath, 1993). In contrast to the tolerance mechanisms mentioned so far, ignorance can be categorized as a “passive” phenomenon. Ignorant, auto-reactive cells are readily activated upon antigen encounter under appropriate conditions (i.e., immunization or viral

infection), but normally persist in the naive pool without contacting their cognate antigens due to spatial separation. As noted above, naive T cells (at least in the adult) recirculate between blood and lymph but do not extravasate from vessels into tissues. The concept of tolerance based on ignorance attributes a central role in the spatial organization of the intact lymphoid system. Accordingly, any sequestered antigen that is neither shed from the cell surface nor released from dying cells should not induce tolerance (anergy, deletion) or auto-sensitize naive T cells. This concept bears the inherent danger that such ignorant, but potentially auto-reactive T cells are activated by cross-reactive pathogens. Once activated, T cells now displaying an "effector" set of homing receptors might be able to penetrate nonlymphoid tissues and mediate immune pathology, a scenario proposed by the "molecular mimicry" model to explain the initiation of autoimmunity (Wucherpfennig and Strominger, 1995).

Regulatory T cells

The mechanisms of T cell tolerance are described by the elimination or inactivation of a given T cell specificity and thus can be defined as "recessive" mechanisms. In addition, there is compelling evidence for the existence of "dominant" mechanisms of tolerance that act via the generation of regulatory T cells. Intriguingly, the dichotomy between central and peripheral mechanisms of "recessive" tolerance seems to hold true for "dominant" tolerance as well, i.e., regulatory T cells can be generated either in the thymus or in the periphery. So-called suppressor T cells were the subject of heated debate for a long time and eventually fell into disrepute. The concept has been resurrected by the unequivocal demonstration of thymus-dependent T cells capable of modulating the function of "conventional" T effector cells in vitro and, more importantly, controlling autoimmune pathogenesis *in vivo* (Thornton and Shevach, 1998; Seddon and Mason, 2000).

The cellular and molecular mechanisms involved in the intrathymic generation and selection of regulatory cells, apart from being dependent on thymic epithelial cells, remain as yet poorly characterized. Likewise, their mode of action, which depends on direct cell-cell contact rather than soluble factors, is not known. In addition to thymus-derived regulatory cells, T cells with similar functional characteristics can be generated in the periphery by various experimental procedures including intranasal or oral antigen administration. The regulatory effect of T cells involved in oral tolerance seems to be at least in part due to the secretion of the "anti-inflammatory" cytokine transforming growth factor. The possibility of inducing antigen-specific tolerance in the adult organism raised some enthusiasm among clinical immunologists. Nevertheless, as a cautionary note, the exact conditions required to reproducibly induce oral/nasal tolerance are not yet clearly defined (Faria and Weiner, 1999). (Table 1)

Table 1. Mechanisms of peripheral T-cell tolerance.

Peripheral T-cell tolerance	Modes of tolerance breakdown
Immune Ignorance	Release of sequestered antigens Aberrant expression of MHC class II Molecular mimicry Epitope spreading
Anergy	Release of inflammatory mediators Increased expression or function of costimulatory Molecules Suppression of IDO
Regulatory T Cells	Release of inflammatory mediators
Apoptosis	Defects in apoptosis signaling Viral apoptosis inhibitors

AUTOIMMUNE DISEASES

Autoimmune disease is a condition that is triggered by the immune system initiating an attack on self-molecules due to the deterioration of immunologic tolerance to auto-reactive immune cells. The initiation of attacks against

the body's self-molecules in autoimmune diseases, in most cases is unknown, but a number of studies suggest that they are strongly associated with factors such as genetics, infections and/or environment (Smith and Germolec, 1999). Autoimmune diseases are pathological conditions identified by abnormal autoimmune responses and characterized by auto-antibodies and T-cell responses to self-molecules by immune system reactivity (Invernizzi and Gershwin, 2009).

Autoimmune diseases are chronic conditions initiated by the loss of immunological tolerance to self-antigens and represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems. The chronic nature of these diseases places a significant burden on the utilization of medical care, direct and indirect economic costs, and quality of life. Almost all ADs disproportionately affect middle-aged women and are among the leading causes of death for this group of patients. With the increasing age of patients, the female-to-male ratio for autoimmune diseases becomes more prominent (Anaya, 2010).

Autoimmune diseases are a group of chronic, relapsing, and sometimes lethal diseases, characterized by a defective immune system resulting in the loss of tolerance to self-antigens and over-expression of auto-antibodies. More importantly, autoimmune disorders often occur during the reproductive years, which may lead to pregnancy loss and infertility (Carvalheiras et al., 2012). A major pathway for autoimmune disease incidence is the body producing antibodies that cause the immune system to attack itself. This attack injures and/or destroys organs, tissues, or cells depending on which autoimmune disease is present. Other autoimmune disease pathways include inefficient central tolerance, activation of autoreactive cells, strongly self-reactive Treg cells and defective nucleic acid sensing (Theofilopoulos et al., 2017).

The development of autoimmune disease is a complex process that involves several checkpoints that affect various cells. Many genetic factors influence the predisposition to and onset of disease (Wakeland et al., 2001). Studies using genetically altered mice have shown that cytokines have a prominent role in autoimmunity (Gorelik and Flavell, 2002). Many studies have shown that glycosylation events, cell-cycle progression and the function of APC are linked to ADs as well (Demetriou et al., 2001).

Two well-characterized ADs are rheumatoid arthritis (RA) and SLE. B cell depletion has significantly contributed to our understanding of the role that B cells play in autoimmunity. RA is a chronic inflammatory autoimmune disorder that affects the synovium of the joints (Feldmann and Maini, 2001). The disease is characterized by periods, known as flares, which lead to joint destruction, deformity and disability, often combined with periods of remission (Lagana et al., 2009).

Lupus is an autoimmune disease that is characterized by hyperactivity of T cell and B cell responses and the formation of auto-antibodies against nucleic acids and their binding proteins. The immune system becomes hyperactive, attacks healthy tissues and causes a global loss of self-tolerance (Choi et al., 2012). The most studied auto-antibody in lupus is antidsDNA although others are also indicative of disease (Fu *et al.,* 2015). There are thought to be two forms of lupus, systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE or discoid lupus), however, current biomarkers are the same between the forms and the only known difference is where the disease manifests (SLE manifests systemically and CLE manifests mainly in the skin). Symptoms of lupus can be seen in a wide range of tissues including joints, skin, kidneys, blood cells, brain, heart and lungs (Wieczorek et al., 2014).

Classification of autoimmune diseases

Traditionally, ADs have been categorized as organ-specific or systemic. The organ-specific ADs may represent examples of normal immune responses that produce disease because they are "misdirected" against a self-antigen or organ. By contrast, in systemic ADs, multiple organs are targets for immune attack, and chronic activation of innate and adaptive immune cells is usually present. SLE is considered to be the prototypic systemic AD. However, it should be noted that the categorization of an AD as organ-specific or systemic is based primarily on clinical observations rather than the expression pattern of the self-antigen that appears to be targeted in the attack (Ray, 2012). (Tables 2 and 3)

Factors related to autoimmune diseases

Genetic factors

The different genetic factors are associated not only with disease susceptibility but also with specific auto-antibodies and disease phenotypes. Several studies have been conducted on this issue, identifying different genetic loci suspected to be involved in systemic autoimmune disease pathogenesis. Genetic factors associated with rheumatoid arthritis (RA) development have been widely investigated. Of these, the human leukocyte antigen (HLA) region contributes to approximately half of its genetic susceptibility, particularly in diseases characterized by the presence of anti-citrullinated antibodies. Notably, a number of alleles in the epitope recognition part of the HLA molecule which is strongly associated with RA share a common string of amino acid residues, the so-called shared epitope. Next to HLA genes, other variants seem to be implicated in RA

Table 2. Examples of organ-specific autoimmune diseases.

Organ-specific autoimmune diseases			
Organ	**Disease(s)**	**Self-antigen**	**Major autoimmune mechanism**
Adrenal cells	Addison's disease	Cytochrome P-450 antigens	Autoantibodies
Red blood cells	Autoimmune hemolytic anemia	Red blood cell membrane proteins	Autoantibodies
Platelets	Idiopathic thrombocytopenic purpura	Platelet antigens (GP IIb/IIIa)	Autoantibodies
Stomach	Pernicious anemia	Gastric parietal cell antigens (H+/ATPase, intrinsic factor)	Autoantibodies/Tcells
Small bowel	Celiac sprue (gluten enteropathy)	Transglutaminase	Autoantibodies/T cells
Thyroid	Hashimoto's thyroiditis	Thyroid cell antigens (e.g., thyroglobulin)	T cells/Autoantibodies
Muscle	Graves' disease	Thyroid-stimulating hormone receptor	Autoantibodies
Muscle	Myasthenia gravis	Acetylcholine receptors	Autoantibodies
Pancreatic islets	Type 1 diabetes	Beta cell antigens (glutamic acid decarboxylase, insulin)	T cells/Autoantibodies
Hepatocytes	Autoimmune hepatitis	Hepatocyte antigens (cytochrome P4502D6)	T cells/Autoantibodies
Bile duct cells	Primary biliary cirrhosis	Intrahepatic bile duct (pyruvate dehydrogenase complex protein)	Autoantibodies/ T cells
Heart	Rheumatic heart disease	Myocardial antigens Basement	Autoantibodies
Kidney/lung	Good pasture's syndrome	Basement membrane antigens (type IV collagen α3 chain) T	Autoantibodies

Source: Ray (2012).

Table 3. Examples of systemic autoimmune diseases.

Systemic autoimmune diseases		
Disease(s)	**Self-antigen**	**Major autoimmune mechanism**
Ankylosing sponkylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	TH1 cells and TC cells, autoantibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Systemic lupus erythematosus	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren’s syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies

Source: Ray (2012).

susceptibility such as the PTPN22, TRAF1-C5, PADI4, and STAT4 genes. Moreover, genetic factors seem to contribute to a disease phenotype, especially in terms of erosive damage. Recent data suggest an association between radiographic damage and polymorphisms of genes encoding TNF, IL-1, IL-6, IL-4, IL-5, OPN, and PRF1 (Ceccarelli et al., 2017).

Regardless of the underlying cause for autoimmunity, predisposition to a given autoimmune response is associated with certain HLA allele(s). If the host’s MHC cannot present an antigen, that antigen cannot elicit a response and would not be an autoantigen in that host. The presence or absence of the appropriate MHC would determine whether the potential auto antigen is presented and the occurrence or otherwise of a response to the antigen (Ray, 2012).

Considering SLE genetic variabilities which were identified so far, it has been demonstrated that the latter accounts for less than half of this disease heritability, by the modest overall effect sizes. In this context, HLA loci, as well as non-HLA risk loci (i.e., STAT4, PTPN22, IFIH1, and TRAF3IP2), have been associated with SLE

susceptibility. Moreover, the disease heterogeneity in terms of clinical manifestations and outcomes has been demonstrated to be associated with specific genetic factors leading to the protean clinical picture. These pieces of evidence allow the possibility of elucidating different mechanisms and pathways accountable for disease manifestations. However, except for lupus nephritis associations with ITGAM and IRF gene polymorphisms, no studies have been designed to identify the genetic variants associated with the development of different SLE phenotypes (Ceccarelli et al., 2017).

Some studies investigated the genetic links to other autoimmune diseases, especially organ-specific ones. Among these, some are regarding the genetic background of primary biliary cholangitis (PBC), an autoimmune cholestatic liver disease, characterized by the antimitochondrial autoantibody positivity and by the accumulation of antigen-specific autoreactive B and T cells targeting biliary epithelial cells (Ceccarelli et al., 2017).

Sex hormones

The effects of sex hormones on susceptibility to auto-immunity have been studied extensively. Androgens and oestrogens can influence the susceptibility and the course of rheumatic diseases. More specifically, androgens in a concentration-independent way suppress cellular and humoral immunity while oestrogen metabolites have been shown to increase B-cell differentiation and activate T cells. Endogenous oestrogen fluctuations (e.g. in pregnancy) and exogenous oestrogens for replacement therapy or contraception enhance susceptibility to autoimmune diseases and may lead to aggravation during the course of the disease (Cutolo and Wilder, 2000).

Women and men have differing immune responses, with women tending to respond to infection, vaccination and trauma with an increased Th2 response, and men tending to respond with an increased Th1 response (Fairweather et al., 2008). This has been replicated in other studies including one where Th1/Th2 ratios were determined for healthy men and women and women had a predominantly Th2 cytokine profile (Giron-Gonzalez et al., 2000).

A striking common feature of many ADs in both humans and experimental animal models is that females are more susceptible to autoimmune conditions than males (Whitacre, 2001). Sex hormones such as estrogens and androgens are believed to play a significant role in the sex-based susceptibility to many ADs. Researchers hypothesize that the expression of hormones or factors associated with the development of sex-specific organs can activate previously tolerant or ignorant lymphocytes. Indeed, in a mouse model of SLE, the administration of estrogen unregulated Bcl-2 in B cells and blocked B cell tolerization (Grimaldi et al., 2002).

Environmental factors

There are numerous cases where one identical twin may have an autoimmune disease while the other doesn't, which signifies that there must be environmental triggers as well as genetic susceptibilities. There has been a marked increase in incidence over the past few decades which must be attributed to changing environmental factors over latent genetic factors, as our genetics as a species are not changing that abruptly (i.e. through evolution) (Gourley and Miller, 2007). Environmental factors are less understood but are thought to act as triggers that initiate and promote disease progression. To date, viral infection, tissue injury, diet, and stress have all been implicated in this process suggesting that there may be a "threshold effect" involving multiple triggers rather than a single trigger for autoimmunity. Time is also important in growth, maturation, and aging tuning the rate and direction of disease progression (Hocking and Buckner, 2022) as indicated in Figure 3.

Chemical agents and drugs

Chemical-induced autoimmune models are actually uncommon. Based on the multifactorial and idiosyncratic nature of ADs, it is not surprising that relatively few compounds have been shown to induce clinically apparent autoimmune or autoimmune-like allergic phenomena in animals. The route of exposure may be of significance in relation to the interpretation and extrapolation of data from animal models to the development and status of human autoimmune diseases. However, it is important to note that routes of exposure used in many animal models (for example, intraperitoneal, intramuscular, subcutaneous) may not be relevant or are artificial routes with respect to typical human exposure (primarily oral, but possibly dermal or inhalation, particularly in occupational settings except for injected vaccines) (World Health Organization, 2006).

Pathogenesis of autoimmune diseases

Multiple arms of the immune system may be involved in autoimmune pathology. Antigens are taken up by APC such as dendritic cells (DC) and processed into peptides which are loaded onto MHC molecules for presentation to T cells via clonotypic T cell receptors (TCR). Cytolytic T

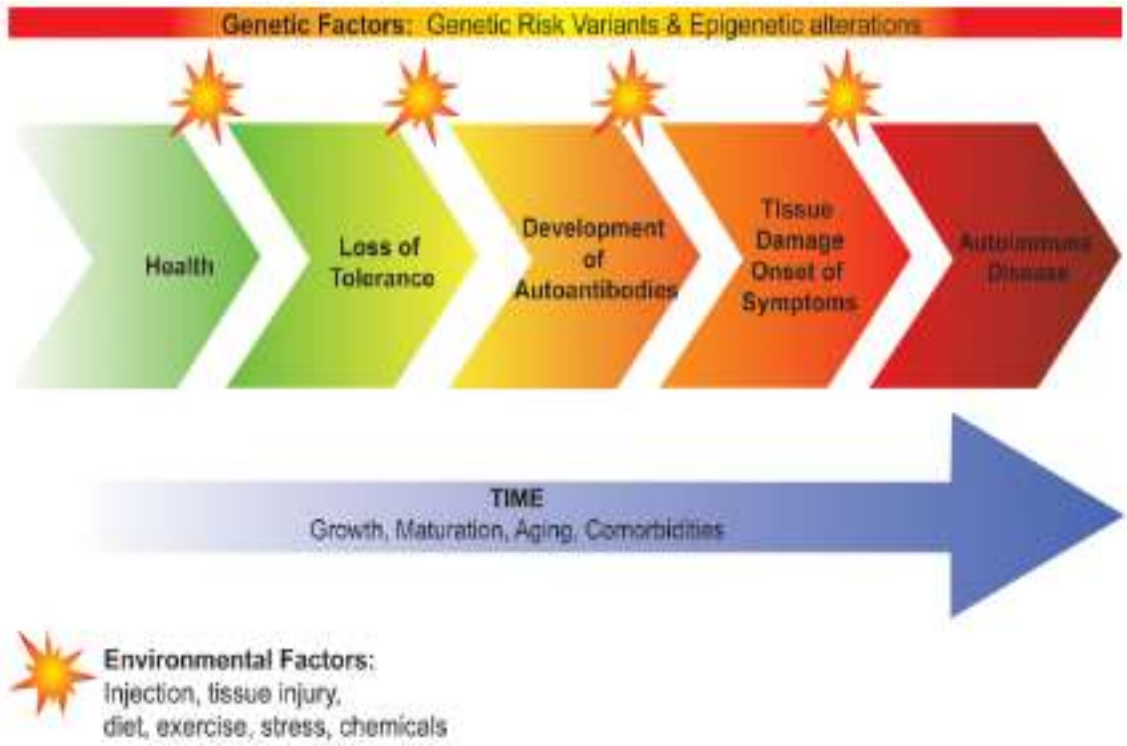

Figure 3. Autoimmunity development and autoimmune diseases progression.

cells (Tc, activated by MHC class I on APC) can directly lyse a target, while T helper cells (Th, activated by MHC class II) release cytokines that can have direct effects or can activate macrophages, monocytes and B cells. B cells themselves have surface receptors that can bind surface antigens. Upon receiving signals from Th cells, B cells secrete antibodies specific to the antigens. An antibody may bind its specific target alone or may bind to and activate macrophages simultaneously via the Fc receptor (Benoist and Mathis, 2001; Wucherpfennig, 2001).

A microbial antigen can include an epitope that is structurally similar to an autoantigen epitope, providing the basic elements of the mechanism referred to as molecular mimicry (Martin et al., 2001). Another mechanism would imply that the inflammatory setting and the paracrine secretion of T cell growth factors induce the expansion of activated autoreactive T cells, whose small number was previously insufficient to drive autoimmune disease. Such a mechanism is referred to as bystander activation (Murali-Krishna et al., 1998).

Autoimmunity prevention mechanism

The immune system has many means of preventing autoimmunity. One mechanism that has gained attention is the action of regulatory T cells. Unlike conventional T cells, which are involved in mounting immune responses, regulatory T cells (Tregs) suppress these responses. Tregs have been pinpointed as key players in avoiding autoimmunity and are currently the subject of intense experimental research (Brusko et al., 2008). Tregs have the capacity to actively block immune responses, inflammation, and tissue destruction by suppressing the functions of an array of cell types including classical CD41-helper T cells, B-cell antibody production and affinity maturation, CD81-cytotoxic T lymphocyte (CTL) granule release, and APC function and maturation state (Mempel et al., 2006).

The immune system has evolved to help protect the body from foreign invading pathogens. To accomplish this critical role, T lymphocytes must discriminate between self and non-self. This property translates into the immune recognition and elimination of infectious invaders while leaving host tissues intact. This highly selective response occurs through several complicated mechanisms to regulate T-lymphocyte activity. The first step is the elimination of self-reactive cells during T-cell development in the thymus. The goal of central tolerance is to achieve a T cell repertoire that is 'self-tolerant.' However, this process is incomplete, and it is well-accepted that autoreactive T cells that escape central tolerance are controlled by peripheral mechanisms (Lohmann et al., 1996).

Autoimmune diseases therapy

In the past years, treatments for ADs have included immuno-suppressive or antiviral/antibacterial treatments. However, therapies that selectively target pathways common to a number of ADs developed later. Therapies include treatments that target proinflammatory cytokines like TNF and IL-1b, block costimulatory molecules, or use therapeutic vaccination with regulatory T cells. Oral medications, such as statins and angiotensin blockers, widely used to treat other disease conditions such as allergies and hypertension, have been shown to inhibit autoimmune inflammation. Since multiple effector mechanisms contribute to the immunopathogenesis of ADs, several effector mechanisms will likely need to be targeted to effectively treat autoimmune diseases (Fairweather, 2007). Since cures are currently unavailable for most autoimmune disorders, patients often face a lifetime of debilitating symptoms, loss of organ and tissue function, and high medical costs (Delogu et al., 2011).

B cell-targeted therapy

In the bone marrow, the immature B-cell central tolerance process takes place. B-cells produce immune globulins which are important for the immune response to various infections. Immunoglobulins come in five classes: IgG, IgM, IgA, IgE, and IgD. Each class has a different purpose in defending the body against different pathogens including viruses, bacteria, fungi and parasites. The membrane-bound version of the B-antibody cells interacts with the antigen on the antigen-presenting cell to activate it. In response to this encounter, B-cell transforms into a plasma cell and secretes significant amounts of certain immunoglobulins that are intended to attack the antigen. This procedure is essential for defense against foreign antigens. However, autoimmunity develops when B-cells identify and remove self-antigens. There are tolerance mechanisms in place to stop this from happening, just like T-cells do (Cuthrell et al., 2022).

TNF blockade and B cell depletion (with anti-CD20) are proven effective therapies for RA. SLE, on the other hand, is a multi-factorial chronic disease that affects multiple organs of the body. A hallmark of the disease is the presence of activated T and B cells that lead to the production of anti-nuclear autoantibodies and immune complexes (Kremer et al., 2005).

Rituxan anti-CD20-mediated B cell depletion

Anti-CD20 mAb (rituxan) therapy represents one of the most successful uses of therapeutic mAbs against a variety of diseases, including chronic lymphocytic leukemia (CLL), indolent (follicular lymphoma) and aggressive (diffuse large B cell lymphoma) types of non-Hodgkin's lymphoma, as well as RA (Lim et al., 2010). The survival of plasma cells in rituxan-treated patients prevents the loss of protective serum antibodies in these patients. The depletion of B cells was initially thought to arise through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) upon binding of anti-CD20 mAb to a cell expressing CD20 (Schiff *et al., 2008)*, and it has also been shown that crosslinking with rituxan can directly induce apoptosis through MAP kinase and p38 (Michaud et al., 2007).

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