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Autoimmune Disorders: An Overview of Molecular and Cellular Basis in Today's Perspective

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Abstract

Autoimmunity arises when immune responses mounted in the host are directed against self-components. Autoimmune diseases are pathophysiological states that result from a loss of self-tolerance and the consequent immune destruction of host tissues. Autoimmunity is mediated by a variety of molecular and cellular events, and responses. The development of an autoimmune disease is a very complex process in which recognition of self-antigens by lymphocytes is centrally involved in pathologic organ damage. Autoimmune disease is inherited as a complex trait, with multiple loci controlling various aspects of disease susceptibility. More recently, some of these susceptibility genes have been identified. Certain environmental influences, such as cigarette smoke, ultraviolet light, or infectious agents, may interplay with this genetic predisposition to initiate the disease process. Silica exposure and its role in systemic lupus erythematosus (SLE) have been identified in studies of occupational exposure, and experimental studies have explored potential mechanisms related to immune dysregulation. Some autoimmune responses emerge following infection by a pathogen, whose protein(s) hold structural similarities to regions on proteins of the host. Thus, antibodies evoked against a pathogen might cross-react with a self-protein and act as autoantibodies, and the concerned autoantigen then provides a source for persistent stimulation. Evidence is emerging that activation of autoimmune B cells and T cells can be influenced by innate immune receptors, such as Toll-like receptors, which primarily recognize pathogen-derived molecular structures but may cross-react with host molecules. Proteins to which the immune system is generally self-tolerant might, if altered, elicit autoimmune responses. Potential involvement of chaperones in the induction of autoimmune disease pathogenesis has also been explored. The contributions of microRNA to pathogenesis of autoimmune diseases like SLE are beginning to be uncovered and may provide us a new arena for exploration of mechanisms responsible for initiation and pathogenesis of autoimmune diseases.

Keywords: Autoimmunity; Autoimmune disease; Self-antigens; Lymphocytes; Autoantibodies; MicroRNA

Introduction

Human autoimmune diseases (AD) occur frequently (affecting in aggregate more than 5% of the population worldwide), and impose a significant burden of morbidity and mortality on the human population [1]. AD are defined as diseases in which immune responses to specific self-antigens contribute to the ongoing tissue damage that occurs in that disease. ADs may be either tissue-specific (e.g., thyroid, β-cells of the pancreas), where unique tissue-specific antigens are targeted, or may be more systemic, in which multiple tissues are affected, and a variety of apparently ubiquitously expressed autoantigens are targeted [2]. Although the definition appears relatively simple in concept, the complexity of this spectrum of disorders is enormous, and has greatly challenged elucidation of simple shared mechanisms. This complexity affects almost every domain, including genetics, phenotypic expression, and kinetics. In the latter case, there is frequently a prolonged period between initial onset of symptoms and development of the diagnostic phenotype, and disease may vary in expression in the same individual over time.

Autoimmunity is not set off by a single cause and is triggered by a variety of agents and molecular and cellular pathways and events. Several elements and mechanisms underlying autoimmune responses have been identified. However, even if a given AD were to be initiated primarily by a single trigger, other events and regulating mechanisms come into play, thereby adding complexity to the process. This review focuses on the current understanding of the mechanistic principles that underlie ADs. We provide an outlook on novel class of immune regulators that play an essential role in multiple pathophysiological processes of multiple ADs.

Overview of Development of Autoimmunity

A major barrier to understanding mechanisms of autoimmunity comes from difficulty in defining early events in these diseases. Since, diseases are only recognizable after development of the diagnostic phenotype, there has been the tendency to interpret findings made at diagnosis with findings present at initiation. Based on recent findings [3-5], the development of ADs can be divided in four phases- i. Susceptibility phase, ii. Initiation phase, iii. Propagation phase and iv. Regulation phase.

The susceptibility to ADs can be either inherited or acquired (and in many diseases, both). ADs result from a complex interplay of pathways and events which initially allow autoreactivity to manifest, and then, after an initiating event, allow development of self-sustaining tissue damage. Factors that trigger the initiation include abnormalities in tolerance induction, regulatory T-cell (Treg) development, or immune signaling thresholds. The propagation phase is marked by a feed-forward cycle of autoimmunity and tissue damage, in which immune effector pathways cause damage and provide antigen to drive the

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ongoing immune response. Figure 1 presents a conceptual framework for the development of AD. It should also be noted that in many cases during disease propagation, immunoregulatory pathways are also activated, which may result in natural inhibition of clinical disease over time. Such immunoregulation is likely absent or fails in a susceptible host.

ADs traditionally have been categorized as organ specific or systemic or both (Table 1). 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.

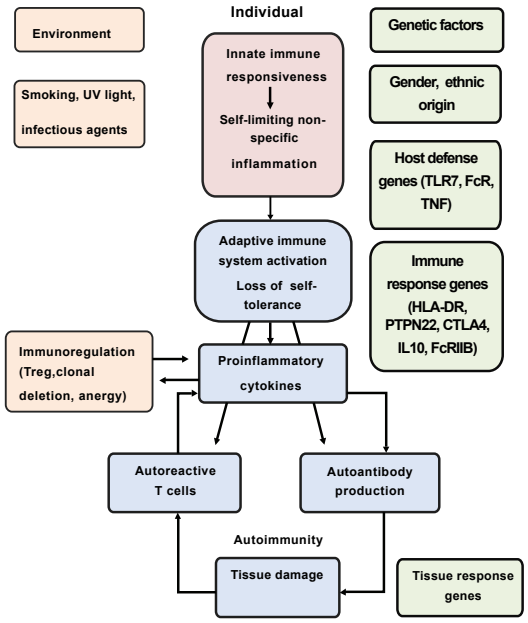

Figure 1: Pathways influencing the development and perpetuation of autoimmune diseases.

Determinants of Autoimmune Disease

Although ADs in humans are genetically complex, significant advances in understanding have occurred over the past several years. For many ADs, the break in peripheral self-tolerance leading to an anti-self immune response is linked to an encounter with a particular pathogen, chemical, drug, toxin, or hormone. However, the single most important factor contributing to AD is the genetic make-up of the host. A complex constellation of AD susceptibility alleles and haplotypes exists that determines the ongoing deregulation of self-tolerance mechanisms.

Genetic predisposition

There have been important advances in the genetics of autoimmunity in several mouse models. These studies highlight a critical role for pathways of tolerance induction, immunoregulation, and setpoints/thresholds for immune signaling in avoiding emergence of autoimmunity [6-8]. It should be emphasized that regardless of the underlying cause for autoimmunity, predisposition to a given autoimmune response is associated with certain human leukocyte antigen (HLA) allele(s). If the host's major histocompatibility complex (MHC) cannot present an antigen, that antigen cannot elicit a response

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/T cells
Small bowel	Celiac sprue (gluten enteropathy)	Transglutaminase	Autoantibodies/T cells
Thyroid	Hashimoto's thyroiditis	Thyroid cell antigens (e.g., thyroglobulin)	T cells/autoantibodies
	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 present
Hepatocytes	Autoimmune hepatitis	Hepatocyte antigens (cytochrome P450 2D6)	T cells/antibodies
Bile duct cells	Primary biliary cirrhosis	Intrahepatic bile duct (pyruvate dehydrogenase complex protein)	Autoantibodies/ T cells
Heart	Rheumatic heart disease	Myocardial antigens	Autoantibodies
Kidney/lung	Goodpasture's syndrome	Basement membrane antigens (type IV collagen α3 chain)	Autoantibodies

Systemic Autoimmune Diseases		
Disease(s)	**Self-Antigen**	**Major Autoimmune Mechanism**
Ankylosing sponkylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	TH_1 cells and T_C cells, auto-antibodies
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

Table 1: Examples of selected human autoimmune diseases.

Autoimmune Diseases	HLA Molecule	Strength of Association
Ankylosing spondylitis	HLA-B27 (Caucasians)	++++
Rheumatoid arthritis	HLA-DR4 HLA-DRB1*04	+++
Systemic lupus erythematosus	HLA-DR2, DR3	++
Sjögren's syndrome	HLA-DR3	++
Psoriatic spondylitis	HLA-B27	+++
Dermatitis herpetiformis	HLA-DR3	+++
Gluten-sensitive enteropathy (celiac disease)	HLA-DQ2	+++
Type 1 diabetes mellitus	HLA-DR3, DR4, DQ2, DQ8	+++
Hyperthyroidism (Graves')	HLA-DR3, B8	+
Hashimoto's Thyroiditis	HLA-DR3, DR5	++
Adrenal insufficiency	HLA-DR3	++
Myasthenia gravis	HLA-B8, HLA-DR3	+
Multiple sclerosis	HLA-DR2	++

Table 2: HLA alleles associated with selected human AD.

and would not be an autoantigen in that host. The presence or absence of the appropriate MHC would determine whether the potential autoantigen is presented and the occurrence or otherwise of a response to the antigen.

Due to their direct involvement in T cell responses, the most important genes that predispose both humans and animals to AD are the MHC genes (Table 2). Perhaps the best illustration of AD-HLA association in humans can be found in ankylosing spondyliitis (AS). Over 90% of Caucasians with AS express an allele belonging to the HLA-B27 family. Other AD also show strong associations with specific HLA allele families. For example, expression of HLA-DR2 and HLA-DR3 predisposes an individual to developing SLE, while T1 diabetes mellitus (DM) has particularly strong links to HLA-DR3, -DR4, -DQ2, and -DQ8. Individuals expressing certain alleles of HLA-DR4 are especially prone to rheumatoid arthritis (RA) or Juvenile RA, while primary Sjogren's syndrome (SS) and polymyositis (PM) are associated with HLA-DR3 in some populations.

The requisite HLA alleles work at the level of antigen presenting cell, whose presence or absence determine the presentation and the resultant response to an autoantigen. However, no genetic pattern is specific to any disease and some patients with specific genetic pattern manifests different diseases. Predisposition of disease can also be seen in families however, phenotypic manifestation can be different.

Environmental triggers

The role of environmental factors in the etiology of ADs is clearly apparent when considering the disease concordance rate between monozygotic twins. More than 50 and sometimes 70 or 80% of monozygotic twins are discordant for major ADs. Despite the existing evidence, however, definitive proof which suggests that that an encounter with an environmental stimulus actually triggers the initial onset of human AD is still lacking.

Environmental stimuli, including chemical agents and pathogens, show significant links to AD onset or flare-ups in both humans and animal models [9]. Certain chemical and pharmaceutical agents have been linked to the onset of particular systemic AD symptoms. For example, toxins such as the heavy metal mercuric-chloride or polyvinyl-chloride can precipitate immune complex nephritis, systemic sclerosis, or the development of autoantibodies. Smoking, use of hair dyes (which contain aromatic amines), glue-sniffing, or exposure to silica dust (as occurs in many types of manufacturing and mining jobs) or other toxins can bring on an episode of RA, SLE, Graves' disease (GD), or scleroderma. Workers in industries such as furniture re-finishing, spray-painting, perfume or cosmetic manufacturing also have a slightly increased risk of developing AD.

Exposure to UV radiation, particularly UV-B rays, has been linked to a physical insult that results in flare-ups of SLE. *In vitro* studies suggest that exposure of DNA and small nuclear ribonucleoproteins (snRNPs) to UV-B results in changes to the conformation and location of these molecules that increase their chances of activating an autoreactive lymphocyte. The mechanism by which these environmental factors induce autoimmunity includes epigenetic changes (DNA methylation and histone modification), reaction with the self component to generate novel antigens, aberrant cell death releasing cellular material that can lead to inflammasome activation and production of pro-inflammatory cytokines and molecular mimicry [10].

Relationship between silica exposure and AD was demonstrated way back in 1914 by Bramwell [11] who showed an increase in the occurrence of scleroderma in stone masons. A study by Sanchez-Roman et al., demonstrated the high probability of workers occupationally exposed to silica developing a multiple spectrum of clinical and serological autoimmune manifestations like SS, scleroderma, SLE, overlap syndrome [12]. Epidemiologic studies have demonstrated moderate to strong associations between occupational silica exposure and SLE. A reduction of Treg cell function and size has been linked to excessive loss of these cells as they become increasingly susceptible to CD95 mediated apoptosis in persons with silica exposure. There is also activation of responder T cells. Taken together, the reduction of Treg cell function and size caused by excessive loss of Treg cells and substitution by chronically activated responder T cells facilitate the immune dysregulation in persons with silica exposure [13].

Some AD may initiate in response to drug treatment. For example, thiol-containing drugs and sulfonamide derivatives, as well as certain antibiotics and non-steroidal anti-inflammatory drugs, appear to trigger the onset of pemphigus. Drugs such as hydralazine and procainamide or similar aromatic amine drugs prescribed can induce SLE-like symptoms such as arthritis, pleuropericarditis, and myocarditis.

Infections with certain viruses, bacteria, and mycoplasma appear to provoke the initiation of systemic AD in genetically predisposed individuals. Moreover, a severe bacterial or viral infection may trigger an increase in autoreactive antibodies or conventional T cells that leads to a flare-up of quiescent AD or an exacerbation of existing symptoms [14,15]. With respect to viruses, the onset of various AD has been variably associated with infection by HSV-1, Coxsackie virus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), human papilloma virus (HPV), or influenza virus. In particular, viral infections have been closely associated with flare-ups of SLE. Similarly, the development of Guillain Barre syndrome (GBS) may follow infection with herpes simplex virus (HSV), EBV, or cytomegalovirus (CMV), and the onset of acute idiopathic thrombocytopenic purpura (ITP) may be preceded by varicella infection. Infections with various bacterial species have also been associated with AD. The most striking example is the development of rheumatic fever (RF) following recovery from infection with a virulent member of the Group A streptococci. Another close link is that between the onset of GBS and *C. jejuni* infection. Antibodies directed against the lipopolysaccharide (LPS) of *C. jejuni* that cross-react with human nerve gangliosides have been isolated from GBS patients.

Infections are major players in the environmental factors which

modulate the development of ADs. Underlying mechanisms are multiple and complex, probably different according to pathogens. It will be extremely interesting to correlate these mechanisms and more generally the infections in question with the polymorphism of genes predisposing to or protecting against the various ADs.

Hormonal influences

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 [16-18]. More than 85 percent of patients with thyroiditis, scleroderma, lupus, and SS are females [19]. In addition to genetic factors such as X-chromosome abnormalities, 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 [20-22]. Disease symptoms were exacerbated in the estrogen-treated animals. Estrogen metabolism is often abnormal in SLE patients, and flare-ups of SLE may on occasion be associated with changes in hormonal status, such as during pregnancy or the initiation of hormone replacement therapy. It is clear that sex hormones have profound influence on immune system development and function. Recent studies revealed that estrogen receptor ERα, rather than ERβ plays a critical role in the regulation estrogen-mediated promotion of autoimmunity in NZB/W mice, [23] and also microRNA (miRNA) induction. Of relevance, the decreased level of miR-146a and miR-125a and increased level of miR-148a have been identified in human patients with lupus and reported to contribute to lupus pathogenesis by regulating type I interferon(IFN) pathway [24,25]. Together, these data suggest that sex hormones such as estrogen may contribute to the pathogenesis of lupus and other gender biased AD via the regulation of miRNA expression.

The two types of autoimmune thyroiditis, Hashimoto's thyroiditis (HT) and GD, also occur predominantly in women. Significant numbers of HT and GD patients first develop their disease in the postpartum period, suggesting that major hormonal changes can precipitate onset. In animal models of hypothyroidism, estrogen exacerbates HT symptoms while testosterone reverses it. Another hormonal influence that may be relevant to AD etiology is the hypothalamic–pituitary–adrenal (HPA) axis. Animals with defects in their HPA axis show increased susceptibility to AD, implying that stress-induced increases in glucocorticoids such as corticosterone and cortisol are required to restrain autoreactive lymphocytes.

Regional/ethnic differences

Many ADs appear to vary in incidence by region or by ethnic group, although such data have been relatively hard to come by and are not consistent for all AD or countries. In some cases, this variation may be due to the uneven prevalence of an HLA allele linked to a particular AD (due to ethnic differences) or of a triggering pathogen or chemical agent (due to geographic or environmental differences). In other cases, the reasons for variation in AD incidence among countries or ethnic groups are not obvious. Tied to the regional/ethnic issue is the observation that the decreasing incidence of infections in western countries and more recently in developing countries is at the origin of the increasing incidence of both autoimmune and allergic diseases including Crohn's disease (CD), T1DM, and multiple sclerosis (MS) [26,27].

Mechanisms Underlying Autoimmune Disorders

The vast majority of AD stem from abnormalities in the mechanisms of peripheral tolerance that fine-tune the repertoires of mature T and B peripheral lymphocytes. The mere presence of autoreactive lymphocytes in an individual's repertoire is not enough to trigger AD: it only predisposes that individual to developing AD. For AD to develop, a stimulus that activates the autoreactive cells must be present, and mechanisms designed to regulate autoreactive lymphocyte responses must fail.

We will now discuss several mechanisms, some of which remain controversial, that are believed to contribute to the development of AD in susceptible individuals.

Pathogen-related mechanisms

The onset or flare-ups of many AD appear to be triggered by particular pathogens. However, one should keep in mind that, apart from infection, there must be other factors involved in AD development because infection is common but autoimmunity is not. Millions of people experience pathogen infections, many of them very serious, but only a small fraction of infected individuals develop AD.

Molecular mimicry: The first pathogen-related hypothesis, called *molecular mimicry* (or *antigenic mimicry)*, holds that autoreactive lymphocytes in the periphery are sometimes activated by cross-reacting pathogen antigens [28-31]. The process of antigen mimicry has frequently been proposed as a potential initiator of ADs (Table 3). This mechanism, particularly when isolated, is only likely relevant to those autoimmune processes clearly associated with antecedent infections, and particularly those that resolve spontaneously. The mechanism may, however, also play a role in initiation of the autoimmune response in self-sustaining autoimmune processes, but in this case, requires that T-cell responses to the cross-reacting self-antigen are initiated.

Foreign antigens, which often differ from their homologous self antigens in some areas, may nevertheless bear significant structural similarity to self-antigens in other regions. Initiation of an immune

Pathogen Antigen	Cross-reacting Mammalian Self Antigen	AD
***Streptococcus* cell wall M protein**	Myosin, other heart valve proteins	RF
Peptides of EBV, influenza virus, HPV, measles virus, HHV-6	Myelin basic protein	MS
LPS of Campylobacter jejuni	Peripheral nerve gangliosides	GBS
Proteins of *Salmonella typhimurium* or *Yersinia enterocolitica*	HLA-B27	Reactive arthritis
Borrelia burgdorferi, OspA protein	Lymphocyte function-associated antigen 1 (LFA-1)	Lyme arthritis
P_2-C protein of Coxsackie virus	Glutamic acid decarboxylase	T1DM
Protein of *Yersinia enterocolitica*	Thyrotropin receptor	GD
B13 protein of *Trypanosoma cruzi*	Cardiac myosin	Chagas heart disease

Table 3: Examples of human autoimmune disease potentially linked to molecular mimicry.

response to the foreign antigen may generate a cross-reactive antibody response that also recognizes the self-protein (antigen mimicry). When the antigen is a cell surface molecule, antibody-mediated effector pathways can lead to host tissue damage. It is important to realize that antigen mimicry alone cannot explain self-sustaining ADs, which are driven by self-antigens and autoreactive T cells. In these cases, there is a requirement for overcoming T-cell tolerance to the self protein. The simultaneous liberation of self-antigen in the presence of the cross-reactive antibody response may allow effective presentation of cryptic epitopes in the self-antigen to autoreactive T cells by activated cross-reactive B cells [32,33]. If continued release of self-antigen occurs, a specific, adaptive immune response to self will be sustained. Antigen release from tissues likely plays a critical role in driving this autoimmune process.

Given the vast number of microbial protein sequences that mimic sequences in human proteins, it is likely that exposure to most microbes does not necessarily trigger an immune response that cross-reacts with human proteins. However, such an initial cross-reactive immune response could lead to subsequent exposure of other regions on the same self-antigen that will then stimulate the emergence of further antibodies, some of them pathogenic, through a process of "epitope spreading".

Induction of inflammation and DC maturation: Infection by a pathogen induces inflammation, supplying "danger signals" and a cytokine milieu that favors dendritic cell (DC) maturation and activation. Many investigators [34-36] have now provided evidence that this inflammation-induced maturation of DCs that may be the key link between pathogen infection and autoimmunity, the so called "adjuvant effect." The hypothesis is that bacterial DNA, bacterial components, and endogenous nucleic acids released upon pathogen-induced cell death are particularly potent adjuvants because they engage the Toll-like receptors (TLRs) of immature DCs. Following TLR engagement, DCs are induced to mature and upregulate their expression of costimulatory molecules. When such mature DCs encounter autoreactive T cells in the lymph node, activation leading to an autoimmune response may result if the pMHC derived from a pathogen or self antigen is recognized by the T cell. Thus, autoreactive T cells that might have been held quiescent due to a lack of costimulation and/or the effector actions of Treg cells regain their capacity for activation.

In humans, increased numbers of DCs can be found in the cellular infiltrates affecting the target tissues in several AD, including GD, HT, RA, T1DM, SLE, and SS. These DCs appear to be mature in phenotype, although it is not clear whether they arrive in the lesions as mature cells or are induced to mature once they arrive. Pathogen-induced inflammation and the release of pathogen-associated molecular patterns (PAMPs) from infected host cells may not be the only way to drive DC maturation leading to AD. Cells that have become necrotic due to mechanical injury, transformation, or other forms of stress may release host stress molecules such as HSP70, HSP60, and gp96 with effects on DCs [37]. While the precise mechanism by which DC function is enhanced by stress molecules remains to be clarified, the results of *in vitro* as well as *in vivo* studies suggest a means by which AD can be induced by endogenous host stress molecules in the absence of pathogen infection.

Microbial superantigens: Another theory to account for at least some episodes of pathogen-linked AD involves microbial superantigens. These molecules can non-specifically activate a large number of different T cell clones by binding directly to particular T-cell receptor (TCR) Vβ sequences [38]. Superantigens are believed to play role in relapses of AD or the exacerbation of existing AD, but they do not appear to be able to initiate AD. In humans, there is evidence that a bacterial superantigen from an unknown species may be a factor in CD. Researchers have also noted that certain TCR Vβ T cell subsets are elevated in cases of Kawasaki disease (KD) and Psoriasis (PS). Indeed, T cells whose TCR Vβ regions are recognized by Group A streptococcal superantigens have been isolated from PS skin lesions.

Disruption in the level or activity of regulatory proteins

The immune system is regulated by complex and intricate cellular and molecular interactions that organize direct and control its functions. Molecular and/or cellular changes that compromise the correct performance of this network have been found to be associated with ADs. Non-HLA genes, including cytotoxic T lymphocyte-associated antigen-4 (CTLA4) gene, protein tyrosine phosphate nonreceptor type 22 (PTPN22), together with other autoimmune susceptibility loci (PDCD1, FCRL3, SUMO4, CD25, PADI4 and SLC22A4), tumor TNF-α and FOXP3 have been associated with susceptibility to ADs [39-42].

CTLA4: CTLA4 is essential for T lymphocyte-mediated immunoregulation. Certain alleles of the CTLA4 gene, encoding a regulatory molecule in the immune system, have been proposed to act as nonspecific costimulatory elements in autoimmunity. Polymorphisms of the T cell regulatory molecule CTLA-4 have been implicated in certain ADs [43], particularly type 1 diabetes [44], autoimmune thyroid disease and lupus [45,46]. A CTLA4 allele has been strongly associated with a type 1 diabetes subgroup with a female bias characterized by failure in tolerance to thyroid peroxidase at an early age [47]. However, the CTLA4 gene is seemingly not a major risk factor or a major determinant of disease progression in primary biliary cirrhosis [48] or ulcerative colitis [49].

PTPN22: The human lymphoid PTPN22 gene encodes an 807-amino acid residue protein referred to as lymphoid tyrosine phosphatase. A single-nucleotide polymorphism (SNP) in PTPN22 has been identified as a major risk factor for several human ADs, including type 1 diabetes, RA, SLE, GD, generalized vitiligo [47,50-53].

FOXP3: FoxP3 is a member of the forkhead family of transcription factors, and is essential for the development of Tregs, which regulate the activation and differentiation of effector T cells at many different levels. Mutations in the FoxP3 gene is associated with emergence of autoimmunity when regulatory T-cell (Treg) differentiation is abnormal in humans with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome [54].

TNF-α: TNF-α is involved in chronic inflammation and autoimmunity [55,56]. For example, TNF-α strongly affects the differentiation of DCs and intraorbital inflammatory macrophages from monocytic precursors. Dysregulation of the TNF/TNFR superfamilies may provide a systemic pathogenic link in GD [57]. T cell clones derived from patients with ADs were found to produce TNF-α, and interaction of TNF-α with type I IFN may contribute to AD development [58].

Alterations in the expression levels of regulatory proteins also cause disturbance of normal functions and produce autoimmune responses. Changes in the level or activity of the regulatory molecular chaperones results in the generation of disordered or misfolded proteins that can become targets of autoimmune responses. Cell-mediated functions of the immune system diminish with age, leading to increased susceptibility to infection and autoimmunity. Disruptions of TCR signal transduction pathways occur in ageing and are believed to be

major causes in the disruption of immune tolerance and expression of autoimmunity.

Altered proteins

Altered proteins can be effective triggers of autoimmunity. Proteins to which the immune system is self-tolerant might, if altered, elicit autoimmune responses. Self-proteins can be altered in a number of ways.

Protein mutation and altered expression: Mutations and altered expression of proteins provide important sources of self-antigens that trigger autoimmune responses. Novel forms of autoantigens generated by mutation, truncation, or splicing. Since the final epitopes generated and loaded on to MHC class II can be profoundly influenced by single early cleavage events during antigen processing, relatively minor but critically placed changes in the primary structure of autoantigens may have the capacity to influence peptide selection. Mutations in the autoimmune regulator (AIRE) gene are responsible for the development of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) [59]. Mutations in the coding part of human mannose-binding lectin increase the risk of infection and autoimmunity [60].

Although, there are not yet good examples where natural autoimmunity arises due to the progressive accumulation of somatic mutations over time, with the expression of mutant, truncated forms of autoantigens, the study by Engelhorn et al. [61] has provide an important mechanistic underpinning for the proposal that accumulated mutations have a role in the initiation of autoimmunity.

Posttranslational modification: Posttranslational modification of self-proteins has an effect on intracellular signalling and protein recognition by the immune system and creates auto-antigens that are not subjected to immune tolerance [62,63]. There is a range of possible post-translational modifications (PTMs) of autoantigens that can allow immune recognition of neo-self epitopes, including phosphorylation, proteolytic cleavage, ubiquitination, transglutamination, citrullination, and isoaspartyl modification [64,65]. An example of a posttranslational modification is the non-enzymatic modification of the carboxyl side groups of aspartate residues to isoaspartyl side chains that causes altered T cell function and autoimmune responses [66,67]. Citrullination of the guanidinium side chains of arginine in proteins by peptidyl arginine deaminase has been implicated in rheumatoid arthritis pathogenesis [68]. There is also evidence that citrullination may play a role in T cell autoreactivity in RA. Immune recognition of citrullinated proteins has also been implicated in MS. In normal CNS tissue a proportion of myelin basic protein (MBP) has citrulline conversions. This proportion has been shown to increase by up to threefold in chronic MS [69]. In several cases, autoantibodies recognize exclusively the modified form of the antigen.

The mechanisms by which PTMs can influence the generation of neo-epitopes for autoimmune attack are complex. These mechanisms can result in a straightforward increase in affinity of binding for MHC or TCR. There can be more subtle effects through altering the susceptibility of a protein to proteolytic cleavage during antigen processing [70]. The extent to which proteins are modified (either spontaneously or enzymatically) can alter as a result of cell stress, inflammation, or infection. The continued dissection of these complex interactions, particularly the effects of infection and inflammatory mediators, is therefore an important area for future research.

Enzyme-processing of proteins: Enzyme-processing of proteins can trigger or amplify specific autoimmune responses. For instance, celiac disease involves immune targeting of glutamine-rich gliadin components of wheat gluten. Deamidation of gliadin by the enzyme tissue transglutaminase (tTG) produces a more potent antigen for stimulation of DQ2-restricted gliadin-specific T cell clones derived from the gut of celiac disease patients [71]. A recent study has shown that while acid deamidated glutens are less allergenic and autoantigenic, enzymatically deamidated gliadins increase these responses [72]. Thus, the manner in which food is processed may be a contributing trigger of ADs.

Disordered proteins: Denatured proteins [73], natively disordered or misfolded proteins can trigger immune responses against self-proteins. Misfolding produces molecular species that have incorrectly-formed three-dimensional structures. Heat-shock proteins and other molecular chaperones assist the correct folding, stabilization, and translocation of proteins. Defects in the function or expression of heat-shock proteins and other molecular chaperones might play a causative role in the stimulation of autoimmunity [74]. Antibodies against heat-shock proteins have been found to recur in ADs [75-77]. Such autoantibodies can interfere with the ability of heat-shock proteins to effect their function in protein refolding.

Sequestered proteins: Sequestered proteins are normally sheltered from immune recognition. However, they can become immunogenic once exposed to recognition by immune cells and induce efficient immune responses.

Several autoimmune disorders have been linked to apoptosis [78,79]. Apoptosis, a process of programmed cell death and removal of damaged cells, results in the release of cell components that are then made accessible to immune recognition.

Apoptosis exposes cytoplasm as well as nuclear components ordinarily sheltered from the immune system. In the presence of defective clearance of cellular debris or subcellular particles, apoptosis can be a significant trigger of autoimmune responses against nuclear components. Proteasome defect resulting from downregulation of expression of a proteasome subunit that prevents the proteolytic processing required for the production and activation of the transcription factor nuclear factor-κB (NF-κB), is reported to play a role in type 1 diabetes [80]. Nucleosomes, which are ordinarily sequestered from the immune system, can, if exposed to immune recognition, become immunogenic and induce autoimmunity, particularly in SLE [81].

Epitope spreading

The determinants that are most efficiently presented are termed 'dominant'; those that are not loaded on to MHC class II to a significant degree are termed 'cryptic.' Epitope spreading is the phenomenon by which immune system appears to expand its response beyond the dominant epitopes recognized by B or T cell to induce new cryptic, non cross-rective epitopes that are recognized much later [82,83]. The appearance of responses to these later epitopes underlies the progression of AD and characterizes its chronic phase. For self-antigens, it is likely that a constant set of dominant determinants are generated during antigen processing under most circumstances, with similar outcomes in the thymus and periphery. Antigens processed by the "standard" pathway are therefore fully tolerized, with the T-cell repertoire purged of reactivity to the dominant self. However, since the balance of dominant and cryptic epitopes is significantly influenced by protein structure, post-translational modification, and folding, changes

of protein structure may alter the balance of dominant and cryptic determinants that are presented during natural antigen processing. The effector actions unleashed during the first response to the original epitope may disrupt cell structure or protein conformation to expose either entirely new self antigens (*intermolecular epitope spreading*) or new epitopes on existing self antigens (*intramolecular epitope spreading*) [84]. It is likely that this paradigm is broadly applicable to autoimmunity, since numerous changes in autoantigen structure occur during various relevant physiological states, and can influence subsequent processing and selection of epitopes presented.

Proven examples of epitope spreading in humans are few. In Pemphigus, blistering of the mouth almost always precedes blistering of the skin, and mouth blisters are associated with the presence of autoantibodies directed against the desmoglein-3 protein. It is not until the attacks on desmoglein-3 expose epitopes on the related protein desmoglein-1 that autoantibodies directed against this latter protein are produced and skin blistering commences. Epitope spreading has also been invoked to account for the polyclonal lymphocyte activation evident in SLE. For example, multiple T and B cell clones reactive to different epitopes of snRNP can be found at different stages of AD progression in SLE patients.

Cellular Mechanisms of Autoimmune Disease

We are all sitting on a minefield of self-reactive cells, with potential access to their respective autoantigens, but since, AD is more the exception than the rule, the body has homeostatic mechanisms to prevent them being triggered under normal circumstances. Initiation of an adaptive immune response requires presentation to T cells of suprathreshold concentrations of molecules with structure not previously tolerized by the host. Such tolerance requires generation of self-determinants in sufficient amounts to be recognized by T cells undergoing deletion in the thymus or anergy in the periphery. It is assumed that the key to the system is control of the autoreactive T-helper cell since the evidence heavily favors the T-dependence of virtually all autoimmune responses.

Role of T cells in initiating and regulating autoimmunity

There is abundant evidence that potentially autoreactive T cells can mature and reach the periphery in most individuals. Numerous "loopholes" in self-tolerance may allow this. Some organ-sequestered antigens are never presented adequately in the thymus. In addition, some self-peptides may not be processed and presented efficiently in the thymus. T cells that escape negative selection against these peptides may be activated in the periphery when these peptides are created by altered proteolysis during inflammation and by post-translational modifications of peptides, such as glycosylation or citrullination [85,86]. Several well-studied animal models are generated by immunization of animals with peripheral organ antigens, such as type II collagen in collagen-induced arthritis and myelin-associated proteins in experimental allergic encephalomyelitis (EAE), which can engender robust T cell responses in the presence of appropriate adjuvants. In addition, immunization of normal mice with nuclear antigens or peptides derived from these antigens can result in lupus-like autoantibody production [87-90]. These experiments indicate that peripheral autoreactive T cells exist and are needed to be kept under control to prevent autoimmunity. Many cellular mechanisms prevent peripheral self-reactive T cells from mediating autoimmune responses (Table 4).

Considerable evidence has emerged in recent years that certain subsets of classic αβ TCR-expressing T cells have the ability to suppress responder T cell proliferation and in vivo T cell responses to self-antigens and foreign antigens [90,91]. Natural Treg cells are a subset of 5% to 10% of peripheral $CD4^+$ cells with a repertoire enriched in self-reactive specificities. These T cells can be identified by their constitutive expression of high levels of the T cell activation marker CD25 and CTLA4. Natural regulatory T cells express a unique transcription factor, FoxP3, which confers many of their properties, such as poor proliferation when activated and the ability to suppress proliferation and cytokine secretion by other T cells activated in co-culture with natural regulatory T cells, in a cell contact-dependent, but non-antigen-specific manner [92]. Genetic deficiency in regulatory T cells secondary to mutations in FoxP3 in the *scurfy* mouse and in humans with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome results in systemic AD, [93] and more recent experiments in animal models show that experimental elimination of regulatory T cells in adult animals can lead quickly to AD [94]. A recent review has linked regulatory T-cell abnormalities with the increased incidence of immuno-inflammatory disease globally [95].

A large body of evidence suggests that T cells are required for the full expression of most rheumatic and other ADs [96,97]. In particular, HLA associations, the presence of infiltrating $CD4^+$ T cells at the sites of pathology in various organ-specific ADs, and evidence for T cell help in the repertoire of autoantibodies all point to a role for T cell help in AD. Pathogenic autoantibodies in SLE exhibit isotype switching and somatic mutation that are hallmarks of T cell help. Most animal models of lupus, type 1 DM, and antigen-induced AD can be prevented and in most cases ameliorated by T cell depletion. However, in humans, this has been difficult to accomplish.

Role of B cells

Multiple checkpoints are involved in the prevention of activation of autoreactive B cells in the peripheral lymphoid tissues [98]. Autoreactive B cells are part of the normal peripheral B cell repertoire, and defects in central B cell tolerance do not seem to be necessary to allow for pathogenic autoantibody production. The escape of autoreactive T cells secondary to intrathymic deficiency of *AIRE* is sufficient for the subsequent development of autoantibodies to multiple organs [99]. The transfer of alloreactive $CD4^+$ T cells and generation of chronic graft-versus-host disease cause pathogenic lupus-like autoantibody production in normal recipient animals [100]. The ability of normal animals to generate diverse antinuclear antibody responses after immunization with one nuclear antigen is further support of this conclusion [88,97]. Similar to regulation of autoreactive T cells, studies suggest that regulation of B cells in the peripheral lymphoid tissues may be important for the prevention of B cell autoimmunity. The therapeutic benefit of depleting B cells in mice and humans has refocused attention on B cells and their role in autoimmunity beyond autoantibody

Peripheral T cell Tolerance	Modes of Tolerance Breakdown
Immune ignorance	Release of sequestered antigens Aberrant expression of MHC class II Increased expression of autoantigen/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

Table 4: Mechanisms of peripheral T cell tolerance.

production, with important functions in cytokine production and antigen presentation [101-103].

Studies in murine lupus have indicated that T cell activation in some circumstances may depend on the presence of B cells [104]; this mechanism may also suggest why B cells are important for continued disease activity in RA. B cells specifically serve as cellular adjuvants for $CD4^+$ T-cell activation, while regulatory B cells, including those that produce interleukin-10, function as negative regulators of inflammatory immune responses. The emerging picture is that B cells, autoantibodies, and T cells are all important components of abnormal immune responses that lead to tissue pathology unique to each AD, with their relative contributions changing during disease progression [103]. The antigen-presenting function of B cells is likely to be important in the broadening of autoantibody repertoire that occurs during the progression of autoantibody disease that is termed *epitope spreading*. Autoantigen-specific B cells can promote epitope spreading because they can internalize macromolecular self-antigen complexes through their autoreactive B-cell receptor (BCR) and efficiently process and present linked autoantigen epitopes to T cells, allowing T cell help to develop against "spread" epitopes [105]. Epitope spreading may explain how a response to one epitope can mature into a full-blown autoimmune response.

ADs where B-cell functions are closely correlated with disease activity include systemic lupus erythematosus, rheumatoid arthritis, scleroderma, type 1 diabetes, and multiple sclerosis. Autoantibodies produced by B-cell-derived plasma cells provide diagnostic markers for autoimmunity but also contribute significantly to disease pathogenesis. Understanding the overlapping roles of B cells as mediators of AD will facilitate the development of more precisely directed therapies.

Influence of antigen presenting and tissue environment on autoimmunity

It has been increasingly evident that the manner and environment in which T cells and B cells are activated can have profound effects on their subsequent differentiation and susceptibility to peripheral tolerance mechanisms [106,107]. Stimuli derived from different pathogens can instruct DCs to differentiate into different subtypes that prime T cells to become different effector subtypes. DCs presenting self-antigen without activation or through alternative activation pathways can induce T cell anergy or promote T cell differentiation into IL-10-producing or FoxP3-positive regulatory T cells. The cytokine TGF-β seems to be crucial for this alternative activation pathway, at least in animal models.

Major differences between tissues in the responsiveness and cytokine secretion patterns of immune and nonimmune cells also are important in the control of immunity and autoimmunity [108]. Target cells in normal tissues express low levels of autoantigens. Under conditions of stress, damage, and exposure to cytokines, antigen levels increase, likely associated with changes in antigen structure (various post-translational modifications). Furthermore, type I IFNs sensitize target cells to killing pathways, maximizing antigen release through apoptosis or other forms of cell death. Autoantigens released from this perturbed target cell have adjuvant capacity. Type I IFNs have multiple effects which conspire to drive additional immune responses to self (including B and T cells), regulate monocyte differentiation into mature antigen-presenting DCs, increase target cell killing, and enhance autoantigen expression. These multiple interacting loops that reinforce each other likely play important roles in generating self-sustaining tissue damage (Figure 2).

The cytokine network

In host defense, Th1 cells primarily enhance cell-mediated inflammatory immune responses, such as delayed-type hypersensitivity reactions, which frequently involve activation of macrophages and effector T cells. The ability to mediate an effective immune response against certain intracellular pathogens seems to depend strongly on the generation of a Th1 response. In contrast, Th2 cells mainly provide help for B cells by promoting class switching and enhancing the production of certain IgG isotypes and production of IgE, including in allergic diseases. T cells producing the cytokine IL-21 also may be important in promoting B cell functions [109] The Th2 cytokines IL-4 and IL-10 also can function to limit macrophage activity [110] and Th2 cells may negatively regulate inflammation in AD.

Although, Th1 cells were associated with organ-specific AD models such as collagen-induced arthritis (CIA), EAE (multiple sclerosis), and other induced diseases, more recent findings in mouse models have shown that another T helper subset that produces the cytokine IL-17 (Th17) is required for the development of many of these diseases, including CIA and EAE [111]. IL-23, a cytokine that shares a common p40 subunit with IL-12, but also uses a unique p19 subunit, is important for the maintenance of Th17 cells, and blocking antibodies against the IL-23-specific p19 subunit or genetic deletion of p19 block the development of CIA, EAE, and T cell–dependent models of inflammatory bowel disease [112-114]. How these different cytokines and T helper subsets influence human AD, is just beginning to be worked out, but it is notable that large amounts of IL-17 can be detected at sites of inflammation, such as rheumatoid synovium [115,116]. Blockade of p40, which makes up IL-12 and IL-23, has proved to be effective in treating human inflammatory bowel disease [117]. Therapies that modulate cytokine production and action are potentially powerful immunostimulants or suppressants and need to be tested with caution, but could be an important addition to the armamentarium of antirheumatic treatmen.

MicroRNA, a New Paradigm for Understanding Autoimmune Diseases

MiRNAs are newly discovered, small, non-coding ribonucleic acids that play critical roles in the regulation of host genome expression at the post-transcriptional level. During last two decades, miRNAs have emerged as key regulators of various biological processes including immune cell lineage commitment, differentiation, maturation, and maintenance of immune homeostasis and normal function [118,119].

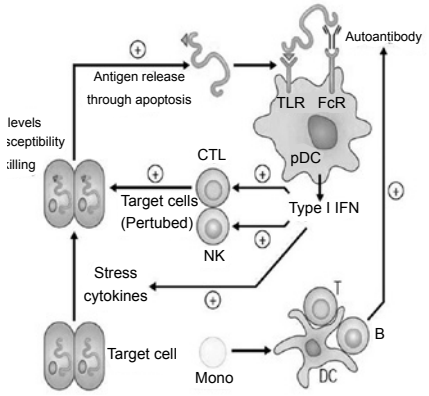

Figure 2: The propagation phase in autoimmune diseases.

Diseases	miRNAs	Pathogenic contribution	Cells
Systemic lupus erythematosus [24,25,129]	miR-146a	Targets STAT-1 and IRF-5, negative regulator of Type I IFN pathway	PBMCs
	miR-148a	Target DNMT1 directly and indirectly, induces DNA hypomethylation and the expression autoimmune-associated genes	$CD4^+$ T cells
	miR-125a	Targets KLF13, Negative regulator of inflammatory chemokine RANTES	PBMCs
	miR-21	Target RAS, induces DNA hypomethylation	$CD4^+$ T cells
Rheumatoid Arthritis [130-134]	miR-146a	Targets FAF1, negative regulator of T cell apoptosis	PBMC, $CD4^+$ T cells, Th-17 cells, synovial fibroblasts
	miR-155	Targets Matrix metalloproteinase (MMP)-3/1 in RASFs, Regulation of inflammation and potentially involved in RASFs mediated tissue damages	PBMC, Th-17 cell, synovial fibroblasts
	miR-124a	Targets cyclin-dependent kinase 2 (CDK-2) and chemokine MCP-1, negative regulator of cell proliferation and MCP-1 secretion	synoviocytes
Multiple sclerosis [135-138]	miR-326	Targets Ets-1, Promotes Th-17 cell differentiation	$CD4^+$ T cells
	miR-17-5P, miR-20a	Potentially involved in the regulation of T cell activation	$CD4^+$ T cells
	miR-34a, miR-155 and miR-326	Targets CD47, promotes phagocytosis of myelin by releasing macrophage from inhibitory signaling	MS lesion

Abbreviation: PBMC: Peripheral Blood Mononuclear Cell; STAT: Signal Transducer and Activator of Transcription; IFN: Interferon; IRF-5: Interferon Regulatory Factor 5; KLF13: Kruppel-Like Factor 13; DNMT1: DNA methyltransferase 1; RANTES: Regulated upon Activation Normal T-cell Expressed and Secreted; FAF1: FAS-Associated Factor 1; RASFs: Rheumatoid Arthritis Synovial Fibroblasts; MCP 1: Monocyte Chemoattractant Protein 1

Table 5: MiRNAs in human inflammatory autoimmune diseases.

This rapidly emerging field has revolutionized our understanding of normal immunoregulation and breakdown of self-tolerance. The powerful gene regulatory role of miRNAs is now well recognized. The expression and function of miRNAs are essential for the development of diverse physiological systems and the maintenance of the cellular homeostasis and normal function [120,121]. The field of miRNA research gained widespread attention with the recognition of aberrant expression and/or function of miRNAs in a broad range of ADs [122-124].

With the increased recognition that miRNAs are capable of controlling the immune cell development and function [125-128], it is conceivable that dysregulated miRNA expression will lead to the immune tolerance breakdown and the development of ADs. Moreover, the unique dysregulated miRNA expression patterns have been identified in human patients with SLE, RA, and MS. Table 5 illustrates selected AD-related miRNAs that have been shown to play critical pathogenic roles in the development of these diseases [24,25,129-138].

The importance of miRNAs to immune system maintenance and autoimmunity is now becoming increasingly clear, owing to concerted efforts invested on mechanistic insight into miRNA roles in AD pathogenesis during the past several years. These findings led to the identification and characterization of numerous novel miRNAs and thereby open up a new perspective on functional mechanism of autoimmune pathogenesis and highlight the possibility of miRNA-based disease interventions.

Conclusion and Future Direction

The development of autoimmune disorder is a complex process. The main molecular and cellular mechanisms of autoimmune responses and their origins are numerous and diverse. Although knowledge regarding different aspects of the immunopathogenesis of these disorders, especially related to animal studies, has advanced dramatically in recent years, major gaps in knowledge of human AD pathogenesis persist. The cellular immunologic abnormalities involved in the initiation and perpetuation of disease also need much greater definition. Better understanding of these processes would also provide new molecular and cellular strategies for control and manipulation of autoimmune responses and diseases. The remarkable increase in information regarding the immune system, and the genetic basis of complex traits, is likely to accelerate the pace of our understanding of human autoimmunity in the near future. Major progresses have been made in understanding of miRNA biology, as well as obtaining insights into its role in pathogenesis of ADs. We anticipate that, the advances made by the application of novel and high-throughput technologies to the analysis of diseased tissues, including miRNA and the autoantibody repertoire, and the development of novel effective miRNA-based gene therapies will make the future of this field very bright.

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