Review

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Overview of Autoimmunity: Classification, Disease Mechanisms, and Etiology

Shanti Narayanappa Koppala, Vaishnavi Guruprasad

People's Education Society University, Department of Biotechnology, Bengaluru, India

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Corresponding Author: Shanti Narayanappa Koppala, People's Education Society University, Department of Biotechnology, Bengaluru, India
Phone: +91 8105188200 **E-mail:** shantikoppala@pes.edu **ORCID:** orcid.org/0009-0006-6780-3379

Abstract

Autoimmunity and its associated diseases have been the primary area of focus in research in the past decade; however, several mechanisms are still left unclear. Autoimmune diseases are idiopathic and currently, there are hardly any genetic tools available to predict who is at risk of developing them. With the advancement of artificial intelligence, it could be possible to predict the potential emergence of autoimmune disorders. This review article discusses the disease classification and relevant causes, including environmental, biological, and genetic factors. Additionally, it explores certain mechanisms where the T-regulatory cells fail and lead to disease development. The article delves into the etiology to illustrate how autoimmune diseases could develop in a person as well as therapeutic approaches are also discussed. With the development of multiplex technologies, it is easier to detect autoantibodies in blood while cytokines and chemokines can give a breakthrough in diagnosis and novel therapeutics for these diseases.

Keywords: Autoimmune disease, T-regulatory cells, B-regulatory cells, autoantibodies, X inactivation

Introduction

Autoimmunity was initially studied by German immunologist Paul Ehrlich, who called it "*Horror autotoxicus*" in the 20th century (1). An autoimmune response is a condition where the body's immune cells do not recognize self-antigens, destroying their cells. In 1965, Macfarlane Burnett introduced not only the concept of autoimmunity but also that of lymphoid cell maturation, thymic instruction, apoptosis, and removal of self-reactive cells in his hypothesis (2). Autoimmune diseases are both rare and chronic. About 80 to 100 autoimmune diseases have been discovered by scientists (3). The exact cause of autoimmune diseases is not fully understood. The autoantibodies are produced against self-antigens as a result of this response. Although the exact reasons for the disease remain unclear, studies suggest various factors, including lifestyle, environmental factors, genetic traits, and hormonal influence. It is important to note that a person with one autoimmune disease is at a higher risk of developing another, as the body's immune system struggles to distinguish between self and non-self-antigens (4). A few observed risk factors for developing autoimmune disease include side effects to certain medications, smoking, exposure to toxins/infections, and obesity (5). Clinical symptoms associated with each autoimmune disorder exhibit variations, ranging from acute organ failure that is life-threatening to persistent chronic illnesses (6). A person with an autoimmune disease typically experiences common symptoms such as inflammation, fatigue, weight loss, abdominal pain, and more. These symptoms usually vary depending on the type of the disease and the individual (7).

Epidemiology

Autoimmune diseases are not very common, but they have a significant impact on mortality and morbidity (2). They appear to be influenced by gender, environmental conditions, and location. Their prevalence is approximately 3-5% in a population (2). They can occur at different ages, and gender biases, ethnicity, and demographics are complex. Women are more prone to autoimmune diseases (8). The exception to this is Crohn's disease, where the ratio

ORCID: S.N. Koppala 0009-0006-6780-3379, V. Guruprasad 0009-0005-1947-004X

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is 1:1.2. The prevalence of autoimmune diseases varies among different ethnic groups and geographic locations (9). Systemic lupus erythematosus (SLE) is common in Asians, African-Americans, and Hispanics (9). Age of onset varies with different autoimmune diseases. The age of onset of autoimmune diseases impacts their prognosis, clinical course, severity, progression, and long-term complications (10). Diseases with early onset are mostly distinctive from those developing in adulthood (10). Diseases like Juvenile idiopathic arthritis and Type I diabetes mellitus (T1DM) are some conditions that portray pediatric onset. Rheumatoid arthritis (RA), Hashimoto's thyroiditis, and multiple sclerosis (MS) typically show late symptoms (10).

Autoimmune Diseases Classification

Autoimmune disorders can be categorized according to the site of their attack, falling into three distinct groups: Systemic, Organ-specific, and Hemolytic (11). Systemic or non-organ-specific autoimmune diseases affect major organs such as the brain, heart, liver, and kidney, by causing the accumulation of immune complexes in tissues, which results in autoimmune diseases (12). Examples include SLE (anti-nuclear Ab) which affects the brain, kidney, heart, lungs, and skin; RA (anti IgG Ab) which affects the joints, heart, and lungs; and MS which affects the brain, muscles, and eyes (12). Organ-specific autoimmune diseases target a particular organ due to autoantibodies. Examples include Hashimoto's thyroiditis affecting the hyposecretion of thyroxine, Myasthenia Gravis affecting the myelin coating of the neuronal axon, and T1DM occurring when the body's immune system attacks and destroys the insulin-producing cells in the pancreas (13). Hemolytic autoimmune diseases are clinical disorders that produce autoantibodies against self-blood components leading to destruction (14). Examples include autoimmune hemolytic anemia, a condition where the body produces antibodies (ab) against its red blood cells, which results in the destruction of these cells, and leukopenia is a condition that causes a decrease in the number of neutrophils due to an autoimmune response (15). Notably, autoimmune leukopenia occurs as a primary condition alongside other autoimmune diseases like SLE, RA, etc.; Thrombocytopenia is characterized by low platelet count due to autoimmune destruction of platelets (15).

Autoimmune diseases can be classified based on the target organ and central systems they affect. These systems include neuronal, cardiovascular, cutaneous, kidney and lungs, musculoskeletal, gastrointestinal, hematopoietic, endocrine, and multiple systems (11). Figure 1 shows different organ systems affected by some autoimmune diseases.

Contributing Factors

Genetic Predisposition in Autoimmunity

Genetic predisposition plays a major yet intricate role in the pathogenesis of autoimmune diseases (16). Some diseases are associated with multiple genes that regulate the immune system while other diseases could result from a single gene mutation that causes the immune system to attack their own cells (6).

Human leukocyte antigen (HLA) molecules are polymorphic (17). Certain genes in the HLA molecule encode proteins involved in the regulation of immune responses and have been shown to be linked with autoimmunity. *HLA* gene variants contribute to an individual's susceptibility to developing autoimmune diseases (18). Some examples are association of *HLA-DRB1* gene with increased risk for RA and HLA-DQB1 & HLA-DR3/DR4 with T1DM (16). Non-HLA has also been identified as a risk factor for autoimmune diseases, such as CTLA-4 and PTPN22 (6).

Studies have revealed that similar genes could increase the risk of different autoimmune diseases (16). In contrast to the above statement, genetic studies could also shed light on the underlying disease mechanisms. An illustrative instance is neuromyelitis optica, which shares clinical similarities with MS but exhibits a closer genetic association with SLE (19). Research in the field of genetics has revealed the influence of ancestry, where individuals of African descent tend to experience a higher incidence of kidney disorders compared to those of diverse ancestries (20). Furthermore, individuals of African ancestry have shown an elevated production of autoantibodies (20).

Most autoimmune diseases are caused due to the involvement of multiple genes, but single-gene mutations do not have lesser impact. This concept can be understood by analyzing the example of SLE due to deficiency in C1q, which plays a primary role in the classical pathway of the complement system (6). The main functions of the complement system include the clearance of immune complexes, so when C1q is deficient, it could lead to the deposition of immune complexes resulting in autoimmunity (21). This could further lead to C3 glomerulonephritis (21). Since C3 is produced from C1q in the subsequent steps, deficiency in C3 causes C3 glomerulonephritis. This indicates that a person with one autoimmune disease is at a risk of getting another autoimmune disease. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is a syndrome caused by a mutation in the AIRE gene (22). This disorder shows Whitaker's triad, i.e., Candidiasis, hypoparathyroidism, and adrenocortical deficiency. AIRE affects the T-regulatory cells causing an autoimmune condition. Interestingly, candidiasis occurs as a result of autoantibodies against interferon leading to immunodeficiency (22). Multiple genes also contribute to disease susceptibility (6). The combined effect of multiple genes increases the risk of developing an autoimmune disease. This is the reason why most diseases are polygenic. Genome-wide association studies have been employed to pinpoint genetic regions associated with autoimmune disorders (16).

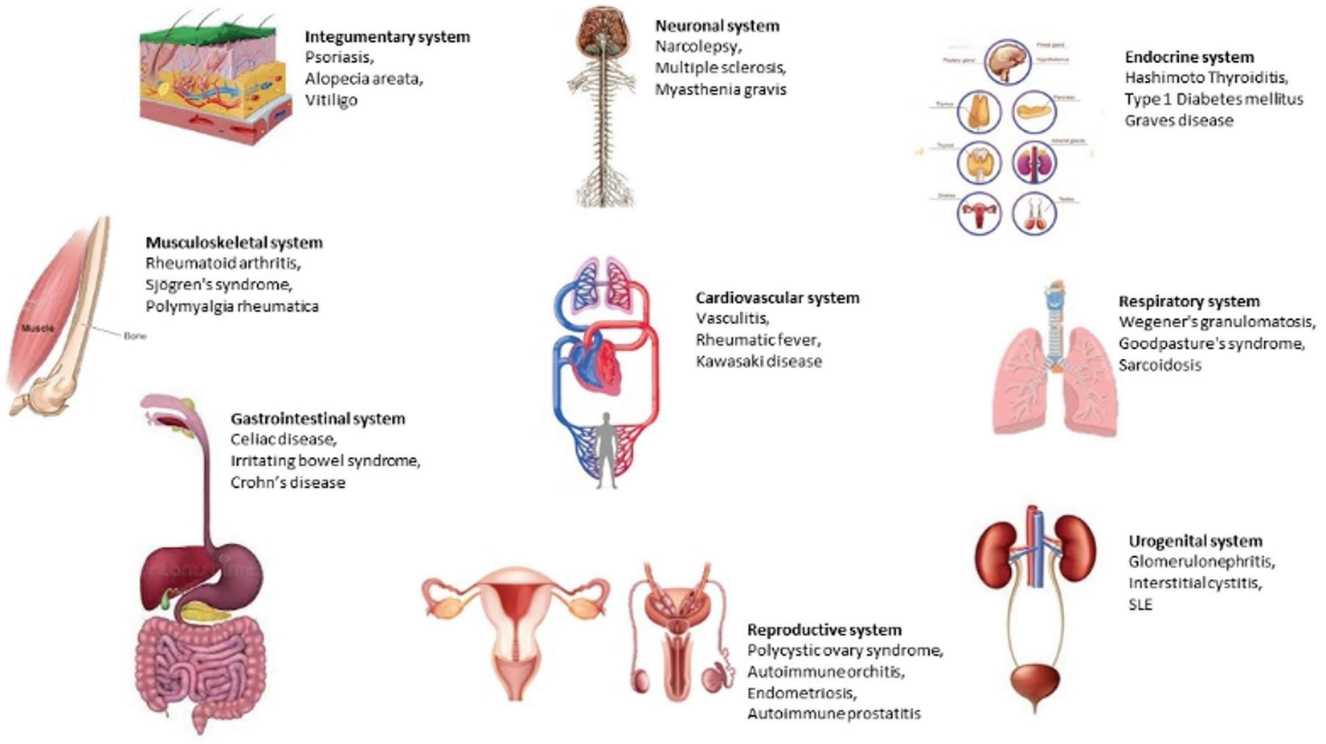

Figure 1. Different organ systems with autoimmune disease.

Environmental Triggers

Studies have shown that environmental factors may influence the pathogenesis of autoimmune diseases like SLE, RA, and Irritable Bowel syndrome (IBS) (23). Many of these environmental triggers induce oxidative stress in the body which is also linked with autoimmunity (24). Some common agents include smoking, mercury, pesticides, and silica. These agents trigger the release of Nrf2, NFκB, and neoantigen formation contributing to the production of autoantibodies and activation of the immune system (24).

Smoking appears to influence RA. It has been observed that nicotine activates PD-1^{-} IL-7R^{+} CD8^{+} T-lymphocytes, which release survivin (25). In the case of SLE, oxidative stress due to smoking causes DNA demethylation and upregulation of inflammatory genes (26). Oxidative stress resulting from cigarette smoking could lead to the generation of autoantibodies, inhibition of T-regulatory cell activity, and enhancement of inflammatory responses (26).

Silica exposure has been associated with SLE, RA, and systemic sclerosis (27). Silica exposure in humans has been linked to the production of anti-nuclear ab, anti-topoisomerase ab, and anti-Fas ab indicative of autoimmune diseases (28).

Pristane, a mineral oil, can cause RA and SLE when exposed to humans (29). Pesticides have also been shown to have an effect, causing SLE based on a study of 12 individuals who were exposed to chlorpyrifos (29).

Photosensitivity refers to an abnormal reaction of the skin to sunlight or other forms of ultraviolet (UV) radiation (30). It can manifest as an exaggerated sunburn response, rash, or other skin symptoms upon exposure to sunlight which could lead to autoimmune diseases (31). Apoptosis is programmed cell death, where apoptotic cells are efficiently cleared by phagocytic cells without triggering the immune system (32). DNA damage from UV radiation causes dysregulation of the immune system and triggers apoptotic cell death leading to conditions like SLE, cutaneous lupus erythematosus (CLE), and polymorphous light eruption (30). Any autoimmune disease results from defects in maintaining tolerances. Similarly, defects in pathways like phagocyte recruitment, clearance of apoptotic cells, and anti-inflammatory signaling fail to maintain peripheral tolerance leading to lupus erythematosus (LE) (31). Evidence shows that patients suffering from SLE and CLE possess an elevated number of apoptotic cells compared to healthy individuals (31). The accumulation of apoptotic cells is a triggering factor causing LE (32). The abnormal activation of apoptosis pathways with CD95 expression for CD95L in serum was increased in SLE patients, which may have led to the excess of apoptotic cells (30). Certain molecules on apoptotic cell surfaces have corresponding receptors on APCs which are cleared in a healthy individual. But when an individual is exposed to UV, the production of apoptotic cells increases, and autoantibodies, as well as cytokines in the microenvironment, interfere in the apoptotic signaling pathway, causing autoimmunity (32).

Biological Factors Contributing to Autoimmunity

Several particular factors that predominantly contribute to the onset of autoimmune disorders encompass biological agents, such as sequestered antigens, neoantigens, cessation of tolerance, loss of immunoregulation, cross-reacting antigens, and molecular mimicry (8).

Sequestered antigens have never been exposed to tolerance mechanisms during the development of the immune system (15). However, any kind of organ injury could lead to the release of these antigens mounting the immune response (33). Some examples include myelin basic protein, sperm antigens post-vasectomy, lens protein after eye damage, and heart muscle antigen after myocardial infarction (33).

Neoantigens are newly formed antigens that arise due to genetic mutations or antigens can be altered by physical/chemical/microbial agents (34). These antigens do not directly cause an autoimmune condition but can influence the development/progression of the disease. For instance, in the case of RA, the presence of citrullinated neoantigen contributes to the production of autoantibodies (35).

Cross-reacting antigens can trigger an immune response against both foreign antigens and self-antigens (36). This occurs when there is a structural similarity or shared epitopes between the foreign antigen and self-antigen, leading to immune recognition and response against both (36). Molecular mimicry is a special type of cross-reactivity where the foreign antigen shares a structural resemblance with the self-antigen (37). In such cases, antibodies produced against the antigen will also attack the self-antigens, leading to autoimmune diseases (37). Examples include rheumatic fever, an autoimmune disease when a person is affected by Group A *Streptococcus* bacteria, the pathogen has a structural resemblance with tissues in the heart muscles (6). The body produces antibodies against the bacteria which will attack the self-antigens leading to rheumatic fever (37). Another example of cross-reacting antigens includes poststreptococcal glomerulonephritis where the streptococcal antigens and the glomerular structures of the kidney share similar epitopes. Hashimoto's encephalopathy has been associated with autoantibodies targeting antigens of both the human brain and sheep brain (6).

Role of Stress in Autoimmunity

Stress is another contributing factor to autoimmune disease. In 1956, Dr. Hans Selye illustrated how stress could lead to autoimmune endocrine diseases (38). Studies have shown that a series of acute or chronic stress episodes induce chronic inflammatory response and metabolic disorders (39). Evidence shows that post-traumatic stress disorders (PTSD) as well as traumatic stress have been linked to conditions like cardiovascular diseases - atherosclerosis, myocardial infarction; metabolic disorders - T1DM, type II diabetes mellitus (T2DM), metabolic X syndrome; gastrointestinal disorders; and musculoskeletal disorders among others (40). Patients with PTSD have shown higher T-cells in blood and lower cortisol levels suggesting that chronic PTSD cases are at a higher risk of developing an autoimmune disease (41). Patients with comorbid PTSD also have higher T-cell counts, higher IgM levels, and lower dehydroepiandrosterone levels, indicating deficient production of hormones, and the presence of biomarkers (41). This suggests that the patient is at risk not only for autoimmune diseases but also for a broad range of inflammatory disease and cardiovascular diseases (41).

Recent studies have identified stress as a developmental factor in a range of diseases, from respiratory and nervous disorders to heart and reproductive health disorders (42). Stress is considered a possible contributing factor for the development of RA (43). Although the mechanism is not fully understood, some aspects include immune dysregulation, inflammatory responses, and certain behavioral changes. Stress-related hormones like cortisol can disrupt the immune system and contribute to disease progression. The presence of chronic stress and elevated inflammatory markers may exacerbate the inflammatory processes in RA, leading to more severe symptoms and disease progression (42).

Bidirectional communication exists between the nervous and endocrine systems and the immune system. Stress can disrupt communication, affecting hormone levels, neurotransmitter function, and immune signaling. These disruptions may influence the immune response and contribute to autoimmune processes.

Disease Mechanism

Autoimmune diseases differ in the way they affect each organ and their clinical manifestations, whether they are systemic or organ-specific. However, it is believed that all autoimmune diseases go through a sequential phase - initiation, propagation, and resolution (44). All these stages are mostly associated with the failure of regulatory mechanisms or some mutation in genes like FOXP3 and are ultimately regulated in the resolution stage by the T-regulatory cells. In the initiation phase, environmental triggers and genetic predisposition play a role. Patients are usually unaware of the symptoms during this stage (44). In the subsequent propagation phase, patients mostly experience cell or tissue damage leading to inflammation. A phenomenon of epitope spreading occurs due to self-protein alterations and damages in tissues and cells, leading to the emergence of new antigenic epitopes (44). Due to the inflammatory environment caused by the autoimmune reaction, many immune cells produce

cytokines and other mediators amplifying the reaction and creating a catastrophic inflammation loop. In this step, the effector T-cells accumulate, triggering the autoimmune reaction (44). The third and final step is resolution where the autoimmune response is brought to control. This is done by the activation of the T-regulatory cells mechanism by FOXP3 (44). This step resolves the activity of the autoimmune response. The activation and resolution mechanisms are explained below.

An autoimmune condition arises when the body's humoral and cell-mediated immune systems fail to distinguish between the self and non-self-antigens, treating the self-antigen as a non-self-antigen and leading to the destruction of the body's own cells (4). Various selection mechanisms eliminate T-cells and B-cells that recognize self-antigens (2). Central tolerance and peripheral tolerances are mechanisms that eliminate lymphocytes which possess receptors that recognize self-antigens (45). Peripheral tolerance is obtained by anergy and suppression by T-regulatory cells. These cells are differentiated from T-cells with intermediate affinity to self-antigens. As mentioned earlier, transcription factors FOXP3 and H10 are upregulated by T-cells, leading to the development of T-regulatory cells that suppress the action of T-cells (46). T-regulatory cells employ different mechanisms to suppress the immune responses. First, they produce anti-inflammatory cytokines like IL-10, IL-35, and TGFβ (47). Additionally, they release perforins and granzymes that damage the target cell membrane, leading to apoptosis (47). Second, the high expression of CD25 and IL-2 reduces the effector T-cell proliferation. CTLA-4 blocks co-stimulation reducing CD80/CD86 expression and it induces the upregulation of indoleamine 2,3-dioxygenase (46). CD39 expression on T-regulatory cells mediates the conversion of ATP to adenosine and AMP, reducing T effector proliferation (47).

Failure of these T-regulatory cells leads to autoimmune diseases (46). This could happen due to a spontaneous mutation, allergies, some metabolic disease, pathogenic infections, hormonal imbalances, etc. (47). Disruption of FOXP3 or mutations in the *FOXP3* genes, and mutations in the CTLA-4 receptors could lead to severe conditions (47).

Certain autoimmune diseases could be fatal while some of them get cured without the person realizing they had one (48). In mouse models, autoimmune inflammation has been observed to be followed by the activation of T-regulatory cells, which controls inflammation and leads to the resolution of the disease (49). However, a flawed generation of T-regulatory cells can lead to the progression of the disease. Various inhibitory receptors have also been observed to reduce autoimmune diseases, such as CTLA-4 and PD-1, which belong to the CD28 family (44). CTLA-4 competes with CD28 to bind to B7 on APCs. This interaction inhibits the activation of T-cells, suppressing effector T-cell function (49). PD-1 is expressed on T-cells and is involved in immune checkpoint regulation helping to prevent autoimmune reactions. PD-1 is increased on T-regulatory cells, enhancing the suppressive function of effector T-cells. PD-1 also limits cytokine production thereby preventing tissue damage (50). Apart from T-cell receptor checkpoints, some B-cell receptor inhibitory pathways are acting as checkpoints. One example is B-regulatory cells, a subset of B-cells having the functions of immunosuppression and regulatory functions (51). These cells maintain immune tolerance, dampen inflammatory responses, and prevent excessive immune reactions, including those associated with autoimmune diseases (52). Another inhibitory receptor acting as a checkpoint in the B-cell receptor is FcγRIIB. CD22 is a co-receptor on B-cells that prevents the activation of self-reactive B cells and contributes to maintaining immune tolerance (52). PD-L1, expressed on B-regulatory cells, interacts with PD-1 on T-cells, resulting in the downregulation of effector T cell responses and preventing the exaggerated reaction of the immune system (53). Dysregulation of PD-L1 expression on B-regulatory cells can lead to autoimmune diseases such as SLE, IBD, T1DM, etc. (54). Targeted autoimmune therapies are based on these immune checkpoints and inhibitory receptor pathways, for example, using CTLA-4 in T-cell receptor and CD22 in B-cell receptor (54).

Certain autoimmune diseases are mediated by stimulating or blocking autoantibodies (55). In some diseases, the autoantibodies bind to the hormone receptor stimulating the hormone activity and leading to the overproduction of the hormone (52). This occurs in the case of Graves' disease, where the long-acting thyroid stimulating autoantibodies bind to the TSH receptor causing excess production of thyroid hormones i.e., thyroxine and triiodothyronine (52). In some other diseases, the autoantibodies bind to the receptor and block their functioning (56). This is illustrated in myasthenia gravis, where autoantibodies to the ACh receptor bind to the ACh receptor blocking the normal binding of acetylcholine at the neuromuscular junction and resulting in abnormal muscle functioning (52).

Another mechanism where the autoantibodies trigger the immune system to cause disease is the formation of immune complexes (6). An immune complex is formed when the antigen attaches to the Fab portion of the antibody (6). When these complexes are deposited in tissue, they activate the complement system, leading to the destruction of antigens and tissue damage due to mast cell degranulation and neutrophil extravasation, causing inflammation in the tissue (57). This mechanism is seen in the case of glomerular nephritis (21). Here, immune

complexes are formed in the blood and are deposited in the basement membrane of the glomerulus. Autoantibodies bind to the autoantigen to a site onto the basement membrane causing glomerular nephritis (21).

Autoimmunity can be triggered by the innate immune system where pathogen-associated molecular patterns are recognized by Toll-like receptors (TLRs) activating innate immune response and inflammatory cascade (58). This affects different types of cells, leading to responses against both self and foreign antigens, which can cause autoimmune diseases (58).

As discussed earlier, certain infections trigger autoimmune diseases through neoantigens or molecular mimicry (34). Animal models have shown many diseases affected by specific antigens like viruses, bacteria, and other pathogens (59). Some common pathogens like cytomegalovirus, Epstein-Barr virus (EBV), *Helicobacter pylori*, and Rubella could trigger the immune system causing diseases like SLE, RA, MS, and T1DM (60). Animal models have shown that EBV can trigger the production of autoantibodies in SLE (59). RA has been seen to be linked to certain bacterial pathogens namely-*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* (59). Human trials have observed RA caused by Hepatitis B virus as well as EBV in RA and Sjogren syndrome (60). Chronic Chagas disease caused by the parasite *Trypanosoma cruzi* may lead to the development of autoimmune myocarditis, although the exact mechanism is not fully understood (60).

In individuals with a predisposition, both Coronavirus disease-2019 (COVID-19) and its vaccine have the potential to instigate the emergence of various autoimmune disorders (61). Antigenic mimicry was observed with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) proteins and autoimmune target proteins (61). The produced autoantibodies can affect not only respiratory and cardiac tissues, but also digestive, skin, and nervous tissues, giving rise to autoimmune diseases (62). The cross-reactivity of SARS-CoV-2 is not limited to humans; it can cross-react with SARS-CoV and possibly other coronaviruses (63). Tissue damage induced by cross-reactive autoantibodies releases more self-antigens, triggering the production of more autoantibodies and leading to an autoimmune response (64). Autoimmunity is initiated when there is a mimicry between the viral peptide and human peptide when they are altered or mutated (65). Infected viral cells release interferon, and damaged tissues undergo apoptosis, releasing self-proteins that cause autoimmunity (66). A range of disorders, such as RA, SLE, and Kawasaki, can develop in a COVID-19 patient (67). Table 1 depicts the categories of autoimmune diseases that can be developed after a COVID-19 infection.

Apart from the disease, vaccines have also shown effects on developing autoimmune diseases (68). Vaccine adjuvants that enhance the immune response may trigger autoimmune diseases (68). Recent studies on the Pfizer and Moderna vaccines, used to treat COVID-19, have shown instances of severe anaphylaxis (69). Some autoimmune diseases like SLE, vasculitis, vitiligo, and alopecia areata may have complications associated with the SARS-CoV vaccine (70,71).

Etiology

In the process of literature review on autoimmune diseases, there were some astonishing facts on autoimmune diseases. This section presents some hypothesis-driven studies with the involvement of autoimmune diseases. These topics shed light on intriguing hypotheses and give valuable insights into the complex nature of autoimmune diseases.

Understanding Gender Bias in Autoimmune Diseases: Prevalences and Mechanisms

Some hypotheses suggest autoimmune diseases affect women with a greater prevalence than men with a ratio of 2:1. Some hypotheses propose the possibility of women getting affected by autoimmune diseases like SLE, RA, psoriasis, etc. It has been shown that autoimmune diseases tend to affect women during pregnancy or hormonal changes (8). Since the real cause of autoimmune diseases is still unknown and multiple factors contribute to the progression of the disease, the following hypothesis can help further our understanding of these diseases. Table 2 depicts the autoimmune diseases that affect women, the age of onset, and the female-to-male ratio.

Two possible reasons for this gender bias in disease susceptibility are X chromosomes and X inactivation (8).

Table 1. Categories of autoimmune diseases that can develop after a SARS-CoV-2 infection

Category	Diseases
Autoimmune blood disorders	Idiopathic thrombocytopenic purpura Autoimmune thrombotic thrombocytopenic purpura, Autoimmune hemolytic anemia
Neurological autoimmune disorders	Encephalitis Cranial neuropathies Guillain-Barre syndrome Myelitis Optic neuritis Acute disseminated encephalomyelitis Multiple sclerosis
Autoimmune ocular disorders	Retinal vein vasculitis occlusion
Renal autoimmune disorders	Crescentic glomerulonephritis Goodpasture syndrome
Autoimmune endocrine disorders	IDDM subacute thyroiditis

IDDM: Insulin-dependent diabetes mellitus

Males and females each possess 23 pairs of chromosomes wherein 22 pairs are autosomes (somatic chromosomes) and 1 pair is an allosome, also known as sex chromosomes. In females, this pair is XX, and in males, it is XY. The X and Y chromosomes significantly differ in size, with the X chromosome being larger and containing a much greater number of genes compared to the Y chromosome (72). The X chromosome harbors approximately 800-900 genes for protein, making up about 5% of the total DNA in human cells, whereas the Y chromosome contains around 50-60 genes coding for proteins, representing only about 2% of total human DNA (73). Due to its larger size and greater number of genes, the X chromosome may harbor a higher likelihood of mutations. Importantly, the X chromosome also contains immune regulatory genes that play a role in inducing immunological responses. The presence of two X chromosomes in females increases their risk of developing autoimmune diseases (74).

X inactivation is a process that occurs during the early stages of embryonic development in a female fetus where overexpression of genes is prevented as genes present on one of the two X chromosomes, in each cell, are silenced (8). In certain cells, the X chromosome inherited from the mother is silenced but, in some cells, the father's X chromosome is silenced. As a result, each cell will genetically vary with respect to its X chromosome (8). In other words, it can be said that some cells may be genetically more skewed towards the maternal X chromosome and others to the paternal X chromosome based on a randomized process (8). In essence, some cells may be genetically skewed toward the maternal X chromosome, while others may favor the paternal X chromosome due to a random process. When cells do not recognize the X chromosome from one parent, it can lead to the generation of antigens (8). If these antigens are not recognized by our immune cells, it can result in the production of autoantibodies, leading to the destruction of cells. This theory appears to underlie the development of SLE (8).

Table 2. Autoimmune diseases that affect women, age of onset, and the female-to-male ratio

Autoimmune disease	Average range for the age of onset	Female: Male ratio
SLE	15-55	7:1
Systemic sclerosis	20-50	3:1
Rheumatoid arthritis	30-60	3:1
Psoriasis	15-35	1.2:1
Sjogren's syndrome	40-60	9:1
Hashimoto's thyroiditis	30-50	10:1
Primary biliary cholangitis	40-60	9:1
Crohn's disease	15-35	1:1.2

SLE: Systemic lupus erythematosus

Exploring the Relationship Between a Strong Immune System and Autoimmune Disease: Evidence and Potential Mechanisms

Andrea Graham, an evolutionary biologist from Princeton University along with her colleagues, has found evidence that people are susceptible to autoimmune disorders (75). The particular reason for this susceptibility is due to their immune system, which is better equipped to combat dangerous infections thereby, enabling them to live longer (75).

Their experimental setup was 1000+ people from Taiwan born between 1892 and 1953 (75). Blood samples were collected from 639 individuals and levels of self-reactive antibodies were measured (75). It was observed that individuals with higher levels of self-reactive antibody were most likely to live longer. Participants with high antibodies had a 33% lower risk of dying in a given year (75). However, it is important to know that these antibodies cause autoimmune diseases. The search team also collected urine samples to check for SLE (75). They found that people with higher levels of autoantibodies were more likely to develop SLE (76).

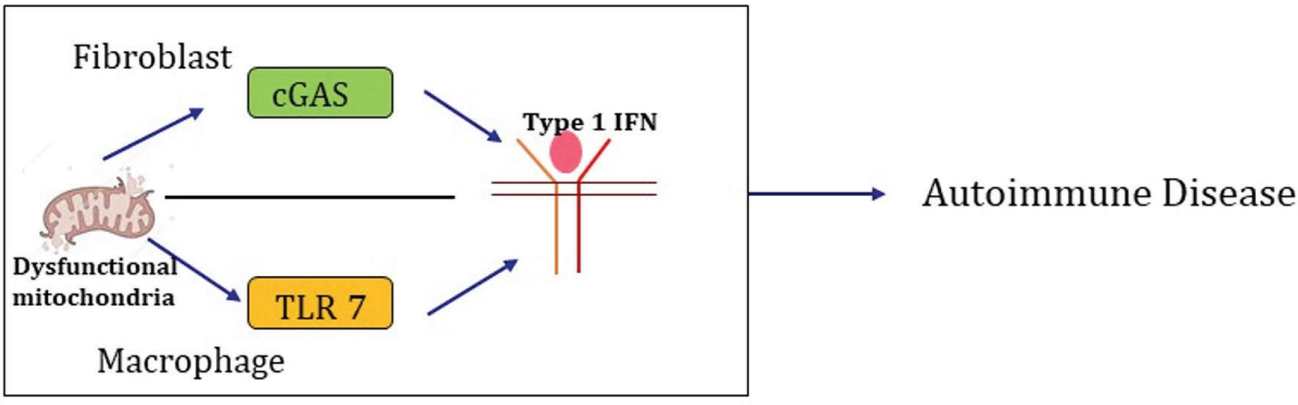

Figure 2. Broken mitochondria spilling RNA and DNA eventually triggers autoimmune disease.

Graham conducted similar research on sheep by analyzing antibodies from blood samples of over 7000 sheep (75). His experiment also suggested that self-reactive antibodies were linked to stronger defense (75).

Gabriel Sorci, an evolutionary biologist at the University of Bourgogne in France, explained that human evolution did not eliminate the autoimmune system (75). Aaron Blackwell an evolutionary anthropologist at the University of California, suggests that if autoimmune were entirely detrimental, the immune system should have evolved to eliminate it (75). This implies that autoimmunity could serve certain functions, and further studies are needed (75).

Several mechanisms have been proposed to explain these findings including molecular mimicry, genetic predisposition, and dysregulation of immune checkpoints. However, it is a complex process that is not yet completely understood. Some experts argue that autoimmunity occurs due to malfunction of immune components rather than a strong immune system.

The Role of Mitochondrial Dysfunction in Autoimmune Disease Development: Evidences, Mechanisms, and Implications

Mitochondria produce energy for the cells to survive, but their origin is rather unusual. Michael Fessler, a senior author at NIEHS, and his research team conducted an experiment in which they removed a gene *IRGM1* in the mice (77). These mice developed an autoimmune condition that resembled Sjogren's syndrome. This condition emerged due to the accumulation of defective mitochondria, leading to the activation of the immune system (77).

The findings of these experiments indicate that failure of mitochondrial quality control may give rise to diseases like Sjogren's syndrome, SLE, and other autoimmune diseases due to the overproduction of inflammatory protein, type 1 interferon, resulting from the accumulation of defective mitochondria (77).

Fessler proposed a mechanism to explain how defective mitochondria could lead to autoimmune disease (77). He stated that "they are descended from ancient bacteria that were co-opted by human cells long ago because they generated energy efficiently". Since bacteria could trigger an immune response, evolution led to these organelles surrounded by layers (77). There are instances where the mitochondria are damaged, leaking their genetic material (RNA and DNA) into the cells. Immune cells recognize these genetic materials as non-self-molecules thereby triggering the immune system to produce type 1 IFN (77).

Prashant Rai, another NIEHS fellow scientist, observed increased mitochondrial DNA in lupus when IRGM1 was knocked out in mice and a Sjogren-like autoimmune disease was cured (78).

Fessler and Rai wanted to determine whether the leakage of mitochondrial DNA triggered the immune system (78). In their validation, they used two different cell types, i.e., fibroblasts and macrophages (78). They observed that in fibroblasts, the leaking DNA activated a receptor called cGAS, while in macrophages RNA receptor TLR7 was activated, mostly due to mitochondrial RNA leakage. Ultimately, both independent pathways produce type 1 interferon, causing autoimmune conditions (77). Figure 2 is a pictorial representation of how dysfunctional mitochondria can cause diseases.

Exploring the Impact of Gluten Allergy on Autoimmune Disease: Development and Mechanism

Gluten is a protein found in wheat, rye, barley, and other food substances (79). It is responsible for soft texture and is made up of two fragments - glutenin and gliadin (79). The former has an adverse effect on the gut and hormone imbalance. The gut produces specific enzymes to break down these proteins. When these enzymes fail to function, gluten is not completely digested, triggering an immune reaction. This is identified as a harmful substance, and antibodies are produced against gluten, causing damage to the lining of the intestine and gut (80). The immune response produces antibodies, such as anti-tissue transglutaminase (tTG) and anti-endomysial antibodies that attack the body's own tissues and cells, resulting in intestinal damage (81). This is the case of Celiac disease.

Effect of Microbiome on Autoimmune Diseases: Mechanistic Connections and Implications

Microbiota consists of different commensal organisms that co-exist, such as bacteria and fungi mostly seen in the mouth, gut, and skin (82). The composition of these organisms differs with the location (82). Any disturbances to these organisms could lead to immune dysregulation (82). Some specific organisms are linked to autoimmune disease. An imbalance in these organisms could disrupt the immune system. In RA, the bacterium - *Prevotella copri* has been found to increase in abundance in the gut of individuals with the disease (82). Interestingly, the peptides produced by this bacterium are similar to self-antigens, which are proteins recognized as foreign substances by our immune cells. These peptides can bind to a specific genetic feature called the shared epitope, which is linked to a higher likelihood of developing RA (83). In SLE, a bacterium - *Ruminococcus gnavus* is found in the gut (82). When *Ruminococcus gnavus* increases in abundance, it can worsen the symptoms of SLE (6).

IBS is a gastrointestinal condition characterized by persistent abdominal discomfort, bloating, and alterations in bowel patterns (84). It is important to note that IBS is not classified as an autoimmune disease, but rather

as a disorder of gut-brain interaction (84). However, promising studies have suggested that the gut microbiome and immune system dysregulation may influence the development and symptoms of IBS (84). In IBS, it is thought that dysbiosis and immune dysregulation may promote inflammation in the gut, increasing the symptoms experienced by individuals (85). Stimulation of the immune system can initiate the release of inflammatory mediators, such as cytokines, which can play a role in hypersensitivity, modified gut motility, and increased sensitivity to pain (86,87).

Diagnosis and Therapeutic Approaches

The diagnosis of autoimmune diseases involves a combination of clinical evaluations, laboratory testing, and imaging techniques (88). The type of diagnostic test is decided by the physician based on the observation of patient's symptoms (88). Evaluating the patient's medical history with family history and genetic disease patterns becomes the primary diagnosis (89). A comprehensive physical examination also plays a major role. Blood tests involve using blood samples to check for certain specific biomarkers which include antinuclear antibody test, C-reactive protein test, erythrocyte sedimentation rate test, complete blood count, and rheumatoid factors. Imaging techniques like X-rays, ultrasounds, computed tomography scans, and magnetic resonance imaging contribute to the secondary diagnosis (90). Certain cases require biopsies of tissues (91). Since inflammation is a recurrent symptom of autoimmune diseases, certain inflammation markers that can be tested are ceruloplasmin, fibrinogen, haptoglobin, and albumin (89).

Therapeutic approaches in autoimmune conditions aim to reduce inflammation using certain anti-inflammatory drugs (92). In certain pathogenic diseases causing autoimmune conditions, it is important to reduce the pathogen-causing symptoms which could reduce the autoimmune condition. This is classically seen in rheumatic fever, where reducing the streptococcal infection becomes the primary treatment. Immunosuppressive drugs are used to suppress the immune system and reduce autoimmune activity (6). However, these immunosuppressive drugs in the long run could suppress immunity and lead to increased risk of tumors and other pathogenic infections. Corticosteroids, which are powerful anti-inflammatory medications, exert immunosuppressive effects on the immune system and control the autoimmune response (93). Currently, cytokine antagonists and tumor necrosis factor (TNF-α) antagonists have shown promising results. Targeted therapies that target several receptors like TNF-α inhibitors, which block TNF-α, reduce autoimmune responses (94). Drugs that block interleukin (IL)-6 and IL-7 modulate immune responses and are very helpful in treating RA and psoriasis. Drugs that block T-cell co-stimulatory receptors like CTLA-4 are popular and are used to treat RA (95). Rituximab, a monoclonal antibody, targets a protein on the surface of B-cells and decreases the production of autoantibodies (96). This is used in the treatment of RA, SLE, and vasculitis. Belimumab, another drug, targets the BLγS and is accepted in the management of SLE (97). B-cell receptor co-stimulatory inhibition using antibodies against CD40L is another approach (97). Ustekinumab, another monoclonal antibody, blocks p40 which is a subunit of cytokine, and has shown good results in the treatment of psoriasis and IBD (98). The inhibition of p40 has revealed the involvement of both Th1 cells and Th17 cells in the progression of the disease (99). Secukinumab, an anti-IL17A monoclonal antibody, can be used in treating ankylosing spondylitis and RA (100,101). Another short-term treatment option is plasmapheresis, which involves the removal of plasma and separation of cells, then reintroduction to the body, which helps in clearing the immune complexes. Certain drugs, initially developed to treat cancer, have shown efficacy in autoimmune diseases by targeting PD-1 and PD-L1, thereby modulating the immune system (102). These drugs include Nivolumab, Pembrolizumab, Durvalumab, and Atezolizumab (103). Research findings indicate that helminths have the ability to modify the immune response, promoting an anti-inflammatory profile that supports the host's survival (59). This is a classic example of co-evolution (59). The best treatment option for hemolytic autoimmune disease is blood transfusion (104). Blood transfusions should be carefully matched to ensure compatibility between the donor and recipient. Another promising approach that has emerged recently is precision medicine. This approach aims to treat the individual based on their unique genetics, environment, and clinical condition where each symptom can be separately treated according to the patient's condition (105).

Several autoimmune diseases self-resolve or exhibit spontaneous remission without any treatment. While the exact mechanisms are not fully understood, there are some hypotheses proposed. The body may regain immune tolerance. There could be changes in the environment contributing to self-resolution (106). In some conditions like alopecia areata and vasculitis, affected tissues have the ability to self-regenerate (107). There is a potential for inherent regulation of the immune system, as well as the modulation of immune responses and the elimination of immune complexes, suggesting the occurrence of spontaneous mechanisms. Some examples that illustrate these conditions include Alopecia areata, vasculitis, SLE, Sjogren's syndrome, Hashimoto's thyroiditis, and dermatomyositis (108).

Conclusion & Future Prospects

The research on autoimmunity and immune response has grown and requires a lot more studies and mechanisms to answer the questions. Novel diagnosis can be made using multiplex technology, and with the development of AI technology in the next decade, we should be able to predict if a person is at a risk of autoimmune disease. This requires a large amount of research and rigorous trials on the existing tests to train the AI for accurate, sensitive, specific, and most importantly inexpensive test results.

Treatments for autoimmune diseases as discussed earlier have been used and some are still under clinical trials. Certain U.S. Food and Drug Administration-approved drugs could be modified using *in silico* tools and checked for target inhibition using molecular dynamics. This could fasten the process of the drug-targeted treatment of autoimmune diseases. The discovery of regenerative medicines in the therapy of autoimmune diseases could be beneficial, exploring stem cell therapies, gene therapies, and medicines for induced tolerance. As mentioned earlier, personalized medicines could be expensive but are a promising approach in the future.

Conclusion

This review paper provides an overview of different aspects of autoimmune diseases, from various disease mechanisms to therapeutic interventions, diagnostic approaches, and novel ideas for the future. Through the etiology, we have realized that autoimmunity could have benefits which include clearing dying cells and other cell debris, facilitating tissue remodeling and tissue growth, immune surveillance of cancer cells, and as an evolutionary selection it could enable it to respond to a wide range of pathogens and environmental challenges. After the global pandemic of coronavirus, autoimmunity could render protection against upcoming global threats. Further research and collaboration are needed to advance our understanding of autoimmune diseases, develop more precise diagnostic tools, and discover novel therapeutic targets to improve patient outcomes and quality of life.

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