

Autoimmune Disease: Pathogenesis

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Autoimmune diseases are a vast array of organ-specific as well as systemic diseases, whose pathogenesis stems from the activation of bursa-derived (B) and thymus-derived (T) lymphocytes reacting against antigens of the body's own tissues (defined as 'self').

Introduction

Autoimmune diseases are the result of specific immune responses directed against structures of the self (Burnet and Fenner, 1949). The organism possesses powerful mechanisms to avoid immune autoaggression. The acquired ability of the immune system to avoid responsiveness to self antigens is defined as 'tolerance', and is obtained by the cooperative efforts of central and peripheral mechanisms, which allow a rapid and efficient removal of pathogens (e.g. viruses or bacteria) in the absence of self-recognition. Occasionally, autoreactive cells may be activated, probably because of molecular mimicry (see below) between structures of the invading microorganism and the self. These autoreactive immune responses, however, are rapidly controlled and shut off by several immunoregulatory mechanisms. Autoimmune diseases, on the other hand, originate from a sustained and persistent immune response against self-constituents, and require a breakdown in tolerance. The mechanisms responsible for this breakdown are so far poorly defined. **See also:** Autoimmune disease; Immunological tolerance: mechanisms; Molecular mimicry

An autoimmune response, usually induced by a triggering event, may be primarily T- or B-cell-mediated, or both. It might, however, be simplistic to define an autoimmune response as B-cell-mediated only. Indeed, whenever immunoglobulin (Ig) G antibody production is initiated, help from CD4⁺ T cells is provided.

In some diseases the autoimmune aggression results in the complete and irreversible loss of function of the targeted tissue (e.g. Hashimoto thyroiditis or insulin-dependent diabetes). In others, the tissue is chronically damaged by the autoimmune reaction, resulting in either hyperstimulation or inhibition of its function (e.g. Graves-Basedow disease or myasthenia gravis). Finally, in other situations, the pathogenic events are multiple and complex, leading to impairment or destruction of several tissues at the same time (e.g. systemic lupus erythematosus (SLE)). **See also:** Autoimmune disease aetiology and pathogenesis

Once the autoimmune reaction is initiated, it is usually self-sustained, leading to the chronic or definitive impairment of the target tissue. The mechanisms underlying the perpetuation of an autoimmune reaction are still obscure,

and this makes the treatment of autoimmune diseases even more complicated.

Breakdown of Tolerance

The concept of autoimmunity has evolved through several historical steps. Paul Ehrlich, at the beginning of the twentieth century, postulated that an immune-mediated mechanism capable of selectively affecting structures of the self was incompatible with life and defined it as 'horror auto-toxicus' (Ehrlich and Morgenroth, 1901). He also performed experiments to demonstrate that it was not possible to induce an autoimmune response in healthy animals. These experiments, however, were repeated by others in subsequent decades in other models, with opposing results. **See also:** Autoimmune disease: animal models; Ehrlich, Paul

Today, it is well accepted that autoimmune reactions are part of the physiological functioning of the immune system. Natural self-reactive antibodies are found at low concentration in the serum of normal individuals (**Table 1**). They usually are of IgM isotype, with low avidity for the antigen. Molecular analyses of the heavy- and light-chain variable regions of natural antibodies show unmutated germline V gene segments, which means that the B cells producing these antibodies have not undergone the somatic hypermutation events characteristic of a T cell-dependent adaptive immune response. Natural antibodies are probably used by the organism to facilitate the clearance of senescent cells and autoantigens, and therefore

Table 1 Characteristics of autoreactive antibodies

Characteristics	Natural antibodies	Pathogenic antibodies
Serum titre	Low	High
Isotype	IgM > IgG > IgA	IgG > IgM > IgA
Antigen specificity	Low	High
V region	Germline	Somatic mutation

Advanced article

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prevent the activation of cognate autoimmune responses. **See also:** Antibodies; Antibody classes; Somatic hypermutation in antibody evolution; Natural antibodies

Autoantibodies involved in the pathogenesis of autoimmune diseases are found at relatively high concentration in patients' sera (**Table 1**). They are usually of IgG isotype, with high avidity for the antigen, and with V regions documenting somatic hypermutations. In other words, these autoantibodies are the product of a T-helper cell-dependent activation of B cells, which mature in conditions of prolonged contact with the antigen and undergo clonal selection.

What is the mechanism that drives the immune system to switch from a harmless natural autoimmune response to the production of very dangerous IgG autoantibodies? The answer is probably within the sophisticated mechanisms that regulate the maintenance of tolerance. Several hypotheses have been formulated to explain the breakdown of tolerance. Some of them are well supported by experimental models.

Tolerance may be broken both at the T- and the B-cell levels. Even though a consistent number of autoreactive B-cell clones is purged during ontogenesis, several autoreactive clones might be generated *ex novo* by somatic hypermutation of V regions during B-cell activation and maturation to plasma cells. Autoantigen-driven B-cell clonal selection, however, cannot take place without the help of cognate CD4⁺ T cells. Therefore, the organism has to ensure that autoreactive T cells are deleted during ontogenesis or induced to tolerance in the periphery. This explains why most of the models of breakdown of tolerance have been studied at the T-cell level (**Table 2**). **See also:** B lymphocytes; Immunological tolerance: mechanisms; T lymphocytes: helpers

Failure to delete autoreactive lymphocytes

The familial association of autoimmune diseases suggests that the aetiopathogenesis of these diseases may be controlled by genetic factors. In certain individuals there might be a genetically determined inability to delete all autoreactive T- and B-cell clones during ontogenesis (Burnet, 1957). Indeed, autoreactive T- and B-cell clones may be detected in the blood of normal individuals. There is no direct evidence, however, that cells directly involved in the pathogenesis of autoimmune diseases originate from these autoreactive clones. The presence of circulating autoreactive lymphocytes in healthy subjects must be considered as physiological. Indeed, tolerance during ontogenesis should not involve the removal of too many self-reactive clones. Due to the frequent molecular similarity between proteins of self and nonself, extensive deletion of potentially autoreactive lymphocytes recognizing autologous antigens would in fact cause a crippling reduction of the T- and

Table 2 Mechanisms hypothesized to be involved in the breakdown of tolerance

Failure to delete autoreactive lymphocytes
Central tolerance failure
Peripheral tolerance failure
Molecular mimicry
Abnormal presentation of self antigens
Aberrant expression of major histocompatibility complex class II molecules
Coupling of self and nonself antigens
Overproduction of self antigens
Disclosure of cryptic T-cell epitopes
Release of sequestered self antigens
Epitope spreading
Polyclonal lymphocyte activation

B-cell repertoire. **See also:** Autoimmune disease: genetics; Immunological discrimination: self/nonself

Tolerance is ensured by several other peripheral mechanisms, which during a lifetime avoid the activation of self-reactive lymphocytes. An inherited impairment of suppressor mechanisms has been postulated, which allows escape of newly generated autoreactive clones (Gershon and Kondo, 1971). Although this issue has long been debated within the immunology community, several pieces of experimental evidence are now available which document the existence of T cells with immunomodulatory activity (Chen *et al.*, 1994; Sakaguchi *et al.*, 1995; Groux *et al.*, 1997).

Molecular mimicry

The number of amino acids from which proteins are made is relatively small and, even though the possible combinations are hundreds of thousands, identical stretches of sequence (less than 10 amino acids) are found relatively frequently among proteins of the body, as well as between self and nonself proteins. Moreover, several proteins are highly conserved phylogenetically, even among very distant species, probably because of their indispensable function within the organism. An immune response may be mounted against a microbial antigen that is similar or identical to a self antigen. The result will be an immune attack against the microorganism and the self tissue. A clinical example of disease caused by molecular mimicry is acute rheumatic fever, in which the antibody response mounted against a group A *Streptococcus* may cross-react with self antigens expressed on articular, cutaneous, cardiac and brain tissues (Stollerman, 1997), leading to the appearance of corresponding clinical manifestations (i.e. polyarthritis, erythema marginatum and subcutaneous nodules, carditis and chorea). **See also:** Molecular mimicry

Abnormal presentation of self antigens

Aberrant expression of major histocompatibility complex (MHC) class-II molecules

In conditions of inflammation, the *in situ* release of cytokines (e.g. interferon gamma (IFN γ)) may induce the expression of MHC class-II molecules on cells that do not usually express such molecules. This phenomenon may allow the presentation of yet unknown self antigens to autoreactive CD4⁺ T cells. This theory is sustained by the evidence that MHC class-II molecules were expressed on β cells and capillaries around the islets of a pancreas from a child who died 24 h after the diagnosis of insulin-dependent diabetes (Bottazzo *et al.*, 1985). It was also shown that, upon viral infection or IFN γ treatment, thyroid epithelial cells expressed MHC class-II molecules (Gaulton *et al.*, 1989). This theory, although fascinating, lacks some corollaries that should explain why naive T cells might migrate within a tissue where they are not expected to migrate, and how they become activated in the absence of costimulatory signals. Nevertheless, the aberrant expression of MHC class-II molecules within the tissue target of an autoimmune reaction might be responsible for an extension or aggravation of an autoimmune inflammatory process. Moreover, this model shifts the concept of autoimmunity from an abnormal T-cell response to an abnormal presentation of self antigens. **See also:** Antigen presentation to lymphocytes; Antigen recognition by lymphocytes; Cytokines; Major histocompatibility complex: human

Binding of exogenous antigens to self antigens

An autoantigen may become coupled to an exogenous antigen which acts as a carrier. In this case, CD4⁺ T cells specific for the exogenous antigen are activated and provide help to B cells specific for the self antigen. Activated B cells act as professional antigen-presenting cells and, by activating anticarrier T helper cells, perpetuate the autoreactive phenomenon. Moreover, owing to the complexity of the antigenic protein, a single carrier-specific CD4⁺ T-cell clone may help multiple B cells, each one specific for different epitopes within the autoantigen. This theory does not require a break of tolerance at the T-cell level, although it does require persistence of the source of carrier in the organism. **See also:** Antigen-presenting cells

Overproduction of autoantigens

Clonal deletion during ontogenesis is more likely to affect autoreactive clones with a high specificity for the antigen. Clones with low affinity for self epitopes may escape clonal deletion and reach the periphery, where they do not become activated because the autoantigens are not sufficiently concentrated to reach the threshold for cell activation. This immunological ignorance may be broken by the release of an excess of autoantigens in the presence of a milieu (e.g.

inflammation), which ensures efficient processing and presentation of those autoantigens. **See also:** Epitopes

Disclosure of cryptic T-cell epitopes

A protein is formed by several amino acid sequences which may represent T-cell epitopes. However, because of the complex mechanisms regulating the processing and presentation of T-cell epitopes, several sequences may act as immunodominant, whereas some others may be cryptic. The former will be readily recognized by T cells, whereas the latter will not, because even if presented they do not reach the threshold for T-cell activation. When this model is applied to thymic selection, it is obvious that the autoreactive T cells deleted during ontogenesis will be those specific for immunodominant epitopes. Autoreactive T-cell clones specific for cryptic epitopes and released from the thymus will be able to circulate freely and harmlessly unless a triggering event subverts the hierarchy of epitopes, and allows presentation of cryptic epitopes. This model received its first experimental support in the work by Gammon and Sercarz (1989). They demonstrated that T cells from adult mice rendered tolerant to whole lysozyme did not proliferate in response to immunization with the whole protein or peptides containing dominant determinants. Conversely, immunization with cryptic epitopes elicited a lysozyme-specific T-cell response.

Release of sequestered self antigens

It is well known that immunologically privileged sites exist within the body (i.e. the brain, eye, testis and uterus), which are usually not patrolled by the sentinels of the immune system. However, once the barrier that hides these tissues is broken, they immediately become targets for autoimmune reactions. A classical example is sympathetic ophthalmia, which is an autoimmune inflammatory aggression to the contralateral eye of a subject who received an eye insult. **See also:** Immunity to infection

Epitope spreading

The phenomenon of epitope spreading was first described by Lehmann *et al.*, 1992, in a model of experimental allergic encephalomyelitis (EAE), which resembles the human disease multiple sclerosis. They showed that mice immunized with a single peptide epitope from the mouse myelin basic protein (MBP) in adjuvant developed a T-cell-proliferative response against the MBP protein, and EAE. A few weeks after immunization, T-cell-proliferative responses against other cryptic epitopes within the MBP were identified in the spleens of animals immunized with the single peptide. These findings suggested that, upon injection of a single T-cell epitope peptide, an MBP-specific CD4⁺ T-cell immune response was initiated, with release of MBP by damaged neuronal cells, and further processing and presentation of epitopes otherwise ignored. Therefore, irrespective of the

nature of the mechanism that allows the presentation of a self epitope, once the self-specific immune response has been initiated it may spread to other self epitopes, previously ignored, for which the deletion of autoreactive T-cell clones is less likely to have occurred in the thymus.

Polyclonal lymphocyte activation

T and B cells may be massively activated in the absence of a nominal antigen. An example is provided by bacterial lipopolysaccharides, which function as polyclonal B-cell activators. Another example is the infection by Epstein–Barr virus. Several autoimmune diseases (e.g. SLE and rheumatoid arthritis) are characterized by a polyclonal B-cell activation, confirmed by the presence of serum hypergammaglobulinaemia and positivity for rheumatoid factors (e.g. IgM reacting with the fragment crystallization (Fc) of IgG). Antigen-independent B-cell activation may also result from an inherited abnormality of B cells. Although polyclonal B-cell activation may be a relevant pathogenic mechanism in systemic autoimmune diseases, it does not seem to be involved in the pathogenesis of organ-specific autoimmune diseases. **See also:** Epstein-Barr virus; Rheumatoid arthritis

Polyclonal T-cell activation has also been hypothesized in the pathogenesis of autoimmune diseases. Several stimuli (superantigens, adjuvants) may activate a large number of T lymphocytes, among which autoreactive clones are nested. **See also:** Superantigens

Antibody-mediated Mechanisms

In 1951, William Harrington, a haematologist, decided to receive an infusion of plasma from a patient with autoimmune thrombocytopenia. He soon collapsed with a seizure, and developed purpura. A blood test demonstrated a sudden drop in platelet count. This crazy and now impermissible experiment represents the first demonstration that autoantibodies can cause human disease.

The possibility of transferring the disease into experimental animals represents one of Witebsky's criteria for the definition of autoimmune disease (the others being the identification of T-cell- and antibody-mediated pathogenic mechanism, and the identification of the autoantigen against which the immune response is directed). Owing to the ease with which autoimmune diseases can be transferred by plasma or serum, and because of the earlier developed techniques for the identification of circulating as well as tissue-bound antibodies, antibody-mediated autoimmune diseases were characterized before and in more depth than T-cell-mediated diseases. **See also:** Autoimmune disease: animal models

According to the Coombs and Gell (1975) classification of hypersensitivity reactions, the antibody-mediated tissue

injury involved in autoimmune diseases may be classified into three types (**Figure 1**) as follows. **See also:** Hypersensitivity (Immunological)

Type-I reaction: immunoglobulin E-mediated diseases

Type-I reactions are characterized by the interaction of an antigen with IgE antibodies bound to basophils and mast cells. This causes the release of soluble proinflammatory factors. Although no direct evidence exists that IgE antibodies are involved in the pathogenesis of autoimmune diseases, IgE specific for self antigens have been identified in several autoimmune diseases of the skin, thyroid, pancreas, eye, connective tissues and joints. **See also:** Hypersensitivity: anaphylactic (Type I)

Type-II reaction: immunoglobulin G or M-mediated diseases

In type-II reactions, IgG (and less frequently IgM) antibodies specific for tissue antigens may cause the disease by several different mechanisms. In the case of autoimmune haemolytic anaemia, IgG specific for antigens expressed on red blood cells (RBCs) may bind to the cell surface and cause cell destruction by activation of the complement cascade, or by clearance of the opsonized RBCs by the reticuloendothelial system, through the interaction with Fc receptors on scavenger cells (e.g. macrophages). A third mechanism involves both complement and macrophages, which in fact may recognize and capture complement-bound RBCs by complement receptors. A similar mechanism operates in the development of autoimmune thrombocytopenia purpura, where platelets are the target tissues. **See also:** Complement: deficiency disease; Hypersensitivity: antibody-mediated cytotoxic (Type II); Immune haemolytic anaemia

It has been demonstrated *in vitro* that natural killer cells (NK) or other Fc receptor-positive leucocytes may kill their targets by antibody-dependent cytotoxicity. However, no evidence is available that this mechanism also operates *in vivo*. **See also:** Natural killer (NK) cells

In pemphigus vulgaris IgG autoantibodies attack epidermal constituents, causing the deposition of complement and the activation of an inflammatory reaction with recruitment of neutrophils, monocytes and other inflammatory cells. In the case of acute rheumatic fever, the antibodies specific for antigens of group A *Streptococcus* cross-react with self-constituents and cause tissue damage by deposition of complement and activation of an inflammatory reaction.

Autoantibodies may also interact with cell surface receptors and cause an aberrant function of the target tissue. In Graves–Basedow disease, autoantibodies bind selectively to the receptors for thyroid-stimulating hormone, causing the uncontrolled production of thyroid hormone

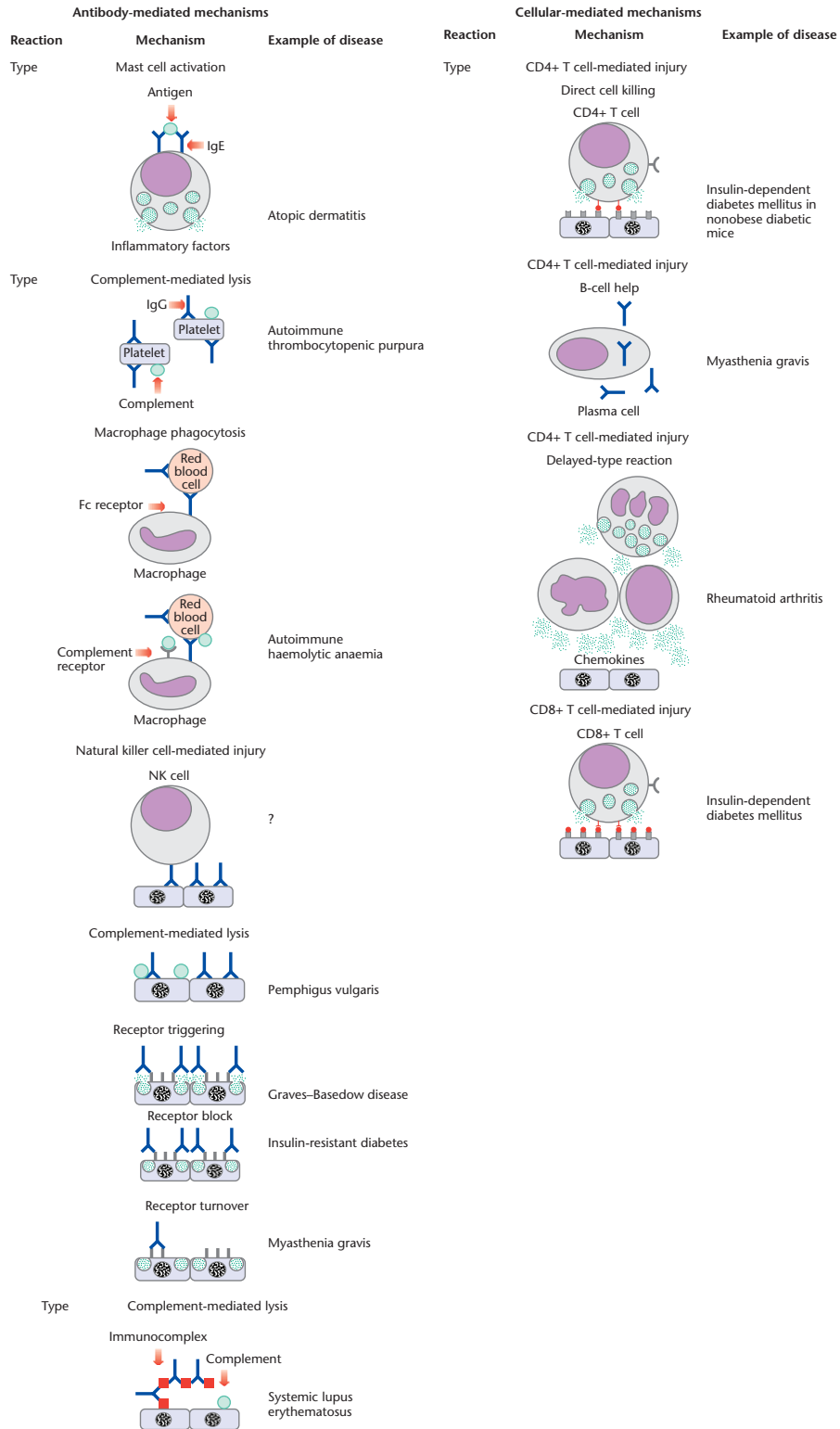


Figure 1 All types of immune-mediated tissue damage may cause autoimmune diseases. See text for details. Ig, immunoglobulin; NK, natural killer; CD, cluster of differentiation.

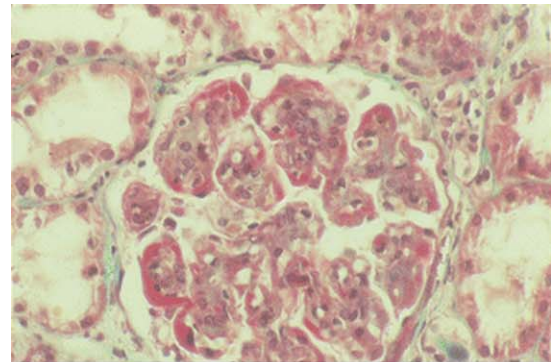
and hyperthyroidism. In insulin-resistant diabetes, which causes hyperglycaemia and ketoacidosis, antibodies resembling insulin compete with insulin and block the function of insulin receptors. **See also:** Thyroid disease

In other pathological situations, autoantibodies may cause tissue dysfunction by different simultaneous mechanisms. Acquired myasthenia gravis is a neuromuscular disease affecting the motor endplate at the neuromuscular junction. It is characterized by muscle impairment and progressive weakness (Conti-Fine *et al.*, 1997). The target of the autoimmune reaction is the acetylcholine receptor located at the postsynaptic membrane. The binding of antiacetylcholine receptor antibodies results in dysfunction of the neuromuscular transmission by at least three different mechanisms. Antibodies may cause the deposition of complement and damage to the neuromuscular junction. They also accelerate endocytosis and degradation of the acetylcholine receptor by antibodies cross-linking two nearby receptors. Finally, antiacetylcholine receptors may directly block the interaction between the receptor and cholinergic ligands. **See also:** Myasthenia gravis; Nicotinic acetylcholine receptors in muscle

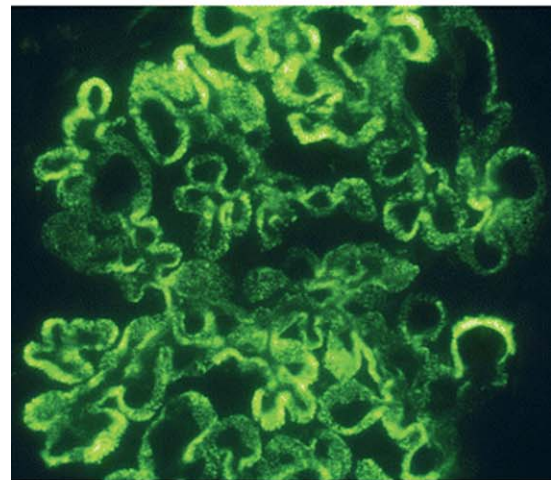
Type-III reaction: diseases mediated by immunocomplexes

Immunocomplexes are produced during an immune response when soluble antigens are available. They are usually cleared by cells bearing Fc and complement receptors and cause no or little damage. When the scavenger system is not efficient enough to eliminate the immunocomplexes (e.g. due to their overproduction or impairment of the function of scavenger cells), and the ratio of antibodies to soluble antigens shows a slight advantage for the latter, immunocomplexes precipitate on tissues more easily. An example may be the serum sickness caused by injection of large amounts of antigens (e.g. hyperimmune immunoglobulins). Serum sickness, however, is a transient disease and, once the immunocomplexes have been cleared, the symptoms disappear. **See also:** Hypersensitivity: immune complex mediated (Type III)

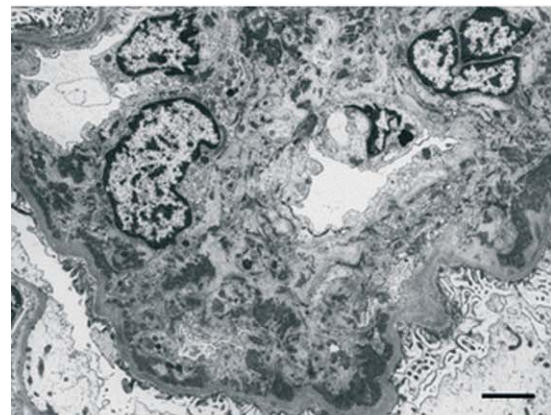
The prototype autoimmune disease caused by immunocomplexes is SLE. SLE is a chronic multisystemic disease characterized by a vast array of symptoms. In contrast to serum sickness, antigens in SLE are produced endogenously and released continuously. Therefore, large amounts of immunocomplexes are produced, which precipitate on the wall of small blood vessels, causing vasculitis and renal damage. Skin rashes, arthralgia and arthritis, and glomerulonephritis (Figure 2) are all clinical manifestations resulting from the deposition of immunocomplexes. The tissue injury caused by immunocomplex deposition is characterized by necrosis-containing fibrin, and cellular infiltrates composed predominantly of neutrophils. **See also:** Immune complex disease; Systemic lupus erythematosus



(a)



(b)



(c)

Figure 2 In systemic lupus erythematosus (SLE), immunocomplexes and complement deposited at the renal glomeruli cause glomerulonephritis. (a) Proliferative SLE nephritis (World Health Organization class IV) with mesangial expansion in all lobules, segmental double contours and abundant, numerous subendothelial linear deposits (AFOG (acid fuchsin orange G); original magnification $\times 125$). (b) Immunofluorescence microscopy showing C1q capillary linear deposits (original magnification $\times 40$). (c) Diffuse subendothelial linear deposits, counterpart to the wire-loop lesion, in a double-contour pattern. Smaller deposits are present in the mesangium. Bar, 2.5 μm (uranyl acetate and lead citrate stain; original magnification $\times 3000$). Courtesy of Dr G Dell'Antonio, H San Raffaele, Milan, Italy.

The most characteristic autoantibodies in SLE are anti-nuclear antibodies, which are directed against deoxyribonucleic acid (DNA), ribonucleoproteins, histones and nucleolar components. Because these antigens are normal constituents of nucleated cells, it has been hypothesized that dysfunction in the mechanisms regulating cell death and the clearance of dying cells are the basis of SLE pathogenesis. Indeed, dysregulation in the induction of apoptosis, clearance of apoptotic cells and secretion of cytokines by scavenger cells has been demonstrated in both SLE and its experimental models. **See also:** Apoptosis: molecular mechanisms

Other models of immunocomplex-mediated diseases are poststreptococcal glomerulonephritis and polyarteritis nodosa, which occur following infection with the hepatitis B virus and the group A *Streptococcus*, respectively. In both cases, immunocomplexes are formed by immunoglobulins specific for microorganism-related antigens, and it is possible to identify exogenous antigens within the immunocomplexes. **See also:** Glomerulonephritis; Hepatitis B virus

Cellular-mediated Mechanisms

The identification of T-cell-mediated autoimmune diseases is a relatively recent discovery. Only in the last two decades, in fact, have methods for the identification of subpopulations and the *in vitro* propagation of T cells become available, which allow the characterization of cells infiltrating the tissue targets of autoimmune reactions or circulating in the blood of autoimmune patients. The use of soluble multivalent MHC/epitope peptide tetramers (Altman *et al.*, 1996; Novak *et al.*, 1999) in particular, is expected to boost the knowledge on the role of T cells in autoimmune diseases. **See also:** T-lymphocytes: helpers

Either one or both CD4⁺ and CD8⁺ T-cell subpopulations may be involved in autoimmune diseases.

Type-IV reaction: CD4⁺ T-cell-mediated diseases

CD4⁺ T cells, by cytokine release, may act either directly against the target tissue or indirectly by delivering help to autoreactive B cells, or activating a delayed-type hypersensitivity reaction. Moreover, cytokines (e.g. IFN γ) released by CD4⁺ T cells may cause alteration in surrounding tissues with abnormal expression of molecules involved in the immune response (see above). CD4⁺ T cells infiltrating the tissue target of an autoimmune response have been demonstrated in myasthenia gravis, Graves-Basedow thyroiditis and insulin-dependent diabetes mellitus in the nonobese mouse. These CD4⁺ T cells appear to be more important in providing help for local production of autoantibodies than in inducing direct tissue damage. It has been postulated, however, that in rheumatoid arthritis,

a chronic inflammatory disease involving mainly the joints, CD4⁺ T cells specific for joint antigens are responsible for the local release of cytokines and inflammation. **See also:** Hypersensitivity: T lymphocyte-mediated (Type IV); Inflammation: chronic

An experimental autoimmune disease in which CD4⁺ T cells have been demonstrated to cause tissue injury is EAE. In particular, EAE can be passively transferred to healthy animals by MBP-specific CD4⁺ T cells.

Type-IV reaction: CD8⁺ T-cell-mediated diseases

CD8⁺ T cells act almost exclusively by killing the target cell. They have been demonstrated to infiltrate the tissue targets of autoimmune reactions. In insulin-dependent diabetes mellitus, CD8⁺ T cells infiltrate Langerhan islets of the pancreas and probably participate in β -cell destruction. There is, however, no evidence of a direct involvement of CD8⁺ T cells in diabetes. More recently, a study indicated that cell-mediated cytotoxic lysis of platelets by CD3⁺CD8⁺ T cells may be involved in the pathogenesis of autoimmune thrombocytopenic purpura (Olsson *et al.*, 2003). **See also:** T lymphocytes: cytotoxic

In mice, a model of autoimmune myocarditis can be induced by infection with *Coxsackie B virus*, with infiltration of myocardial tissues by CD8⁺ T cells.

Initiation and Progression of the Pathogenic Process

Autoimmune reactions are common phenomena during the development of a cognate immune response. The characteristic of these events, however, is that they stop immediately once the exogenous triggering antigen is eliminated.

An autoimmune disease occurs, however, when the immune reaction has grown sufficiently to sustain itself even in the absence of exogenous antigen. As several workers have at least partially suggested in the past, and as Matzinger articulated as a theory in 1994 and demonstrated later (Ridge *et al.*, 1996), the immune system does not really seem to discriminate between self and nonself, but between what is or is not dangerous. The immune system recognizes the antigen, irrespective of whether it comes from an exogenous or an endogenous protein, but depending on whether it is properly presented (i.e. at a sufficiently high concentration and in the presence of costimulatory signals). Danger signals (e.g. tissue stress, death or destruction) allow, by virtue of activation of professional antigen-presenting cells, the efficient presentation of self antigens that were previously ignored by the immune system. Therefore, autoimmunity may be seen less as a defect in the immune response and more as the way in which the

self antigen is presented. The theory of 'danger' (Matzinger, 1994) combines most of the hypotheses described above on how the breakdown of tolerance is obtained and maintained, and explains many of the remaining doubts. How the danger signal is maintained still remains to be clarified. Indeed, in this model, it must be hypothesized that professional antigen-presenting cells continue to present self- or cross-reacting exogenous antigens efficiently. **See also:** Immunological danger signals

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