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ESSENTIALS Autoimmune diseases occur when a sustained, specific, adaptive im- mune response is generated against self-components, and results in tissue damage or dysfunction. They probably affect more than 3% of Western populations, more commonly women than men, and have peak incidence in the third to sixth decades. Aetiology and pathogenesis These can usefully be described in terms of (1) susceptibility— inherited or acquired defects in pathways required to maintain tolerance to self-antigens render the individual susceptible to dis- ease initiation; (2) initiation of autoimmunity—interaction between susceptibility genes and environmental events initiate an immune response directed at self-antigens; (3) transition—targets of im- mune response change and are amplified, with clinical symptoms assuming a recognizable phenotype; and (4) propagation—specific immune response to self-antigens causes damage of tissues, with the release of more antigens that further drive the immune response. Although a single immune effector pathway may predominate in generating tissue dysfunction and damage in some autoimmune diseases, it is much commoner for multiple effector pathways to participate in generating the final phenotype. Those pathways which generate tissue damage or dysfunction include autoantibody binding to target cells, immune complex-mediated activation of complement and Fc receptor pathways, cytokine pathways, as well as lymphocyte-mediated cytotoxicity of target cells. The nature and sites of tissue damage determine the pathological and clinical fea- tures of specific diseases. Tissue-specific autoimmune diseases Immune-mediated damage is restricted to a particular tissue or organ that specifically expresses the targeted antigen (e.g. (1) Graves' disease—autoantibodies bind to and stimulate the TSH receptor, re- sulting in thyrotoxicosis; (2) myasthenia gravis—autoantibodies target the acetylcholine receptor at the neuromuscular junction, resulting in muscular weakness and fatigue due to the inefficient transmission of the acetylcholine signal; (3) type 1 diabetes—a cytotoxic T-cell re- sponse to the β cells of the pancreatic islets results in destruction of the insulin-producing cells). Systemic autoimmune diseases Typically characterized by simultaneous damage in multiple tissues (e.g. kidney, lung, skeletal muscle, nervous system, and skin). Unlike autoantibodies in tissue-specific autoimmune diseases, which target tissue-specific antigens, the autoantibodies in systemic autoimmune diseases are frequently directed against intracellular molecules ex- pressed ubiquitously in multiple tissues (e.g. (1) aminoacyl-tRNA synthetases—targeted in autoimmune myositis and associated inter- stitial lung disease; (2) small nuclear ribonucleoproteins—targeted in systemic lupus erythematosus; (3) topoisomerase-1—targeted in scleroderma). Each of these molecules is expressed in all cells, where they play critical roles in essential cellular processes (e.g. protein translation, mRNA splicing, and DNA replication and remodelling, respectively). Nonsustained autoimmune diseases Organ or tissue damage and dysfunction tend to be self-

limited and resolve after the first attack, and are very unlikely to recur (e.g. epi- demic Guillain–Barré syndrome). These diseases typically occur in the setting of infection, and are associated with cross-reactive im- mune responses that recognize both components of the infecting organism as well as the target tissue. Introduction The effector mechanisms that the immune system utilizes to destroy extracellular pathogens, or cells that either harbour intracellular for- eigners (e.g. mycobacteria or viruses) or become malignant, must be appropriately targeted if indiscriminate damage to normal host tissue is to be avoided. Under most inflammatory circumstances, some bystander tissue damage is unavoidable. In most situations, this damage is self-limited, due to efficient clearance of the exogenous antigen source and appropriate downmodulation of the immune response. Tissue damage in autoimmune diseases differs funda- mentally from bystander damage, in that the host immune system is specifically activated and driven by self-components, focusing damaging immune effector pathways on host tissues expressing those components, in an autoamplifying and self-sustaining way. 4.6 Autoimmunity Antony Rosen

380 SECTION 4 Immunological mechanisms The danger inherent in initiating a self-sustaining, specific immune response directed against components of self-tissues is intuitively apparent, since antigen clearance under these circumstances is ne- cessarily associated with complete tissue destruction. It is now clear that an autoimmune component is a feature of many human diseases. Indeed, there are some estimates that auto- immune diseases afflict more than 3% of Western populations, and imposes a significant personal and economic burden on individ- uals and nations. This chapter will illustrate many of the principles unifying various autoimmune states, and will present a conceptual framework within which to understand their aetiology, pathogen- esis, and pathology. The rapid advances in knowledge being made in this group of disorders predict that disease mechanisms will soon be more clearly understood, and will greatly impact therapeutics. Epidemiology Autoimmune diseases may affect individuals at all stages of life. In general, diseases have a predilection for beginning after the second decade, with peak incidence in the third to sixth decades. In many instances, there is a preference for the female gender, with the mag- nitude of this sex difference varying among the different diseases. Thus, for the systemic autoimmune diseases (e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren’s syndrome, scleroderma, and autoimmune myositis), and autoimmune thyroid disease, the female:male (F:M) ratio is approximately 4–9:1, while for type 1 diabetes, multiple sclerosis, and myasthenia gravis, the female predominance is much less prominent (F:M ratio <2:1). The exact mechanisms underlying this female predominance remain unknown, but this striking biological difference provides a major clue to pathways underlying susceptibility to autoimmunity. Recent studies describing possible gender-related differences in Toll-like receptor (TLR) expression may be relevant in this regard (see fol- lowing section). Aetiology An important theme related to the development of various auto- immune diseases has emerged in recent years. One of the most unexpected observations came from studies of patient popula- tions in whom blood samples had been stored for a period of years prior to the onset of clinical disease (military cohorts or stored blood bank samples), allowing investigators to address whether autoantibodies are first generated coincident with clinical disease, or precede this. In a landmark study by Harley and colleagues in SLE, clear evidence was obtained showing that the relatively ‘non- specific’ antinuclear autoantibodies and antiphospholipid anti- bodies generally precede the diagnosis of SLE, often by a period of several years. These investigators also showed that phenotype- specific autoantibodies in SLE (e.g. anti-Sm, anti-RNP) occurred around the time of onset of clinical disease, suggesting that

dif- ferent autoantibody specificities were marking different phases in the disease. Similar observations have been made in rheumatoid arthritis, where anticyclic citrullinated peptide antibodies pre- date clinical symptoms, whereas more specific antibodies (e.g. antivimentin) only occur when disease becomes established. It is therefore operationally useful to divide autoimmune diseases into separate kinetic phases: 1. Susceptibility—predisease, in which inherited or acquired de- fects in pathways required to maintain tolerance to self-antigens render the individual susceptible to disease initiation; 2. Initiation of autoimmunity—the interface of susceptibility genes and unique events associated with changes in the struc- ture of autoantigens (e.g. mutation or novel post-translational modification), which initiate an immune response directed at self-antigens—this phase is generally not accompanied by clin- ical symptoms; 3. Transition—during which the targets of immune response change and are amplified, and during which clinical symp- toms assume a recognizable phenotype. This generally occurs subacutely over weeks to months, and frequently begins with nonspecific symptoms and signs. Examples include the fatigue and constitutional symptoms that predate diagnosis of SLE and rheumatoid arthritis. This transition phase has important impli- cations for early diagnosis and intervention. 4. Propagation—a self-amplifying phase in which the specific im- mune response to self-antigens causes damage of tissues, with the release of more antigens, which further drive the immune response. It is important to note that this last, amplified phase does not manifest initially fully developed, but rather evolves over time towards the diagnostic phenotype. Both genetic and environmental factors play important roles in ini- tiation and propagation of autoimmune diseases. They probably play their central roles by regulating the activation, function, and targets of the host immune system. There is also evidence that sto- chastic processes play an important role in disease initiation, greatly complicating studies to define the causes and mechanisms of auto- immune disease (see next).
Genetic factors Although autoimmune diseases in humans are genetically com- plex, significant advances in understanding have occurred over the past several years. In some cases, advances have come from the study of autoimmunity with mendelian patterns of inheritance (e.g. APECED, IPEX, C1q deficiency—see definitions to follow). Advances have also come from genetic association studies of various autoimmune phenotypes (e.g. rheumatoid arthritis, SLE, type 1 dia- betes). Together, the studies stress that multiple genes interact in ren- dering an individual susceptible to autoimmunity, and highlight a critical role for pathways of tolerance induction, immunoregulation, and setpoints/thresholds for immune signalling in avoiding emer- gence of autoimmunity.
A reciprocal role of target tissue pathways (e.g. antigen structure/expression) in regulating autoimmunity has also been recognized. The following are some general prin- ciples regarding the genetics of autoimmunity that have emerged in recent years. Certain major histocompatibility complex (MHC) class II alleles are associated with disease susceptibility One of the most striking genetic associations with autoimmunity resides in the MHC, an area on chromosome 6 in humans which is highly enriched in genes that participate directly and indirectly in the immune response. The strength of association of different

 autoimmune phenotypes with MHC class II genes in this area is very robust (odds ratios in the 3–8 range). For example, patients with rheumatoid arthritis have an increased frequency of HLA DR4. HLA DR4 (initially defined serologically) encompasses numerous different alleles that have been defined by sequencing. Interestingly, not all subtypes of HLA DR4 are associated with an increased fre- quency of rheumatoid arthritis, but those alleles that are associ- ated with rheumatoid arthritis share a short amino acid sequence (QKRAA) at positions 70 to 74 of the β chain of the HLA DR mol- ecule. This sequence, termed the ‘shared epitope’, is located along

the peptide-binding groove of HLA DR4 which presents peptides to the antigen receptor of T cells. Interestingly, this same ‘shared epitope’ is present in many HLA DR1-positive individuals with rheumatoid arthritis. A similar principle appears to hold for patients with type 1 diabetes, where there is a strong association of disease with specific DQβ genotype. Since MHC class II molecules function as a scaffold for presenta- tion of specific peptides to CD4T cells (see next), it is possible that this MHC-encoded susceptibility to disease reflects the ability of these alleles to present unique self-peptides to autoreactive T cells. The presence of significant linkage disequilibrium within the MHC region (i.e. large stretches of DNA do not undergo recombination, generating functional cassettes of associated genes) also creates the potential for the disease-association of particular MHC alleles to be influenced by additional genes on the extended haplotype in affected individuals. Studies to define these other genes, and the mechanisms whereby they influence development of autoimmunity, are challen- ging, and are ongoing in many diseases. Incomplete thymic tolerance induction predisposes to autoimmunity Significant insights into basic mechanisms can derive from the study of rare human phenotypes. This has been true for auto- immunity, where several monogenic disorders have defined im- portant pathogenic principles. Autoimmune polyendocrine syndrome type I (APS1; OMIM 240300), also called autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is a rare disease in which patients develop multiple autoimmune diseases, often beginning in childhood. The syndrome is character- ized by striking autoimmunity directed against multiple different target tissues, including parathyroids, adrenals, pancreatic β cells, parietal cells, thyroid, liver, and gonads. Numerous autoantigens have been defined as targets of autoimmunity in APS1, and in- clude enzymes specifically expressed in various endocrine tissues (e.g. steroid 21-hydroxylase—specific for adrenal cortex; steroid 17a-hydroxylase—found in adrenal cortex and gonads, GAD65— found in pancreatic islets, and thyroid peroxidase). The genetic basis of APS1 was mapped to a gene on chromosome 21q22.3, sub- sequently termed AIRE (for autoimmune regulator). AIRE expres- sion is highest in the thymus, where it is expressed in medullary thymic epithelial cells. Significant evidence has now been obtained that AIRE is a transcriptional regulator, which regulates expression in thymic epithelial cells of various peripheral autoantigens nor- mally expressed exclusively in endocrine target tissues. Thus, AIRE appears to regulate the ectopic expression in the thymus of tissue- restricted autoantigens, and provide an antigen source against which to establish central tolerance. Several AIRE-deficient mouse models were subsequently generated; these animals developed various autoimmune endocrine phenotypes, resembling those found in human APS1. Impaired clearance and tolerance induction by apoptotic cells: Susceptibility defect in systemic autoimmunity Although little is known in humans about the thymic pathways of tolerance induction to ubiquitously expressed autoantigens, there is accumulating evidence to suggest that in the periphery, apoptotic cells play an important role in providing a source of autoantigens against which the organism becomes tolerant. Apoptotic cells are generally very efficiently cleared by phagocytic cells; these events are normally associated with the production of anti-inflammatory cytokines and result in tolerance induction. Interestingly, early components of the classical complement pathway (e.g. C1q and C4) and C-reactive protein are required for efficient apoptotic cell clearance, with production of interleukin (IL)-10 and transforming growth factor β (TGFβ). It is of particular note, therefore, that homozygous C1q deficiency is associated with a striking suscep- tibility to SLE, suggesting that rapid, efficient, tolerance-inducing clearance of apoptotic cells may play a similar role to AIRE ex- pression in the thymus in preventing subsequent emergence of autoimmunity to ubiquitously expressed autoantigens. Additional support for this model comes from studies of milk fat globule-EGF factor 8 (MFG-E8), a glycoprotein secreted from macrophages that is required for the efficient

attachment and clearance of apoptotic cells by macrophages and immature dendritic cells. MFG-E8 is also expressed in tingible-body macrophages at the germinal centres of secondary lymphoid tissues. Interestingly, many unengulfed apop- totic cells are present in the germinal centres of the spleen in MFG- E8-deficient mice, which develop a striking lupus-like phenotype. Other examples exist in which defects in clearance of apoptotic cells are associated with development of systemic autoimmunity (e.g. Mer deficiency). Together, the data strongly suggest that efficient, anti-inflammatory clearance of apoptotic cells plays a central role in tolerance induction and prevention of autoimmunity. Defective production of regulatory T cells Although pathways exist that (1) regulate autoantigen expression at sites of tolerance induction, and (2) guide autoantigens towards tolerance-inducing outcomes, these pathways alone are clearly in- sufficient to prevent the emergence of autoimmune disease. This fact is highlighted by the emergence of autoimmunity when regu- latory T-cell differentiation is abnormal in humans with IPEX syn- drome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; OMIM 304790). IPEX is a rare X-linked reces- sive disorder, which is characterized by type 1 diabetes, thyroiditis, atopic dermatitis, and inflammatory bowel disease, and is caused by mutations in the FOXP3 gene. FOXP3 is a member of the forkhead family of transcription factors, and is essential for the development of regulatory T cells (Tregs), which regulate the activation and dif- ferentiation of effector T cells at many different levels. It is therefore likely that induction of tolerance is incomplete under most circum- stances, and that self-sustaining autoimmunity is normally limited by Treg function. Signalling thresholds and susceptibility to autoimmunity Several modulators of T-cell signalling have also been defined as im- portant susceptibility determinants in autoimmunity. For example,

 CTLA4 polymorphisms are associated with increased risk of a var- iety of autoimmune diseases, including type 1 diabetes, Graves' disease, SLE, and rheumatoid arthritis. Similarly, a functional poly- morphism in PTPN22 has been identified as a major risk factor for several human autoimmune diseases, including SLE, rheuma- toid arthritis, and type 1 diabetes. Although the exact mechanisms underlying susceptibility to autoimmunity remain unclear, in both cases the polymorphisms appear to regulate the balance of stimu- latory and inhibitory signalling in effector and regulatory T cells, favouring effector T-cell activation. The genetic studies in autoimmunity therefore highlight that there are many barriers to the development of autoimmunity, including effective tolerance induction in the thymus and periphery, tightly regulated immune signalling, and homeostatic pathways of immunoregulation to limit self-responses should these occur. There are also cassettes of immune response genes encoded in the MHC which appear to be more likely to capture specific self-antigens and generate a response to them. It is likely that the genetic suscepti- bility to autoimmunity in outbred humans represents an integrated threshold involving genes that regulate these various pathways, upon which environmental and stochastic events act to accomplish disease initiation and propagation. Environmental factors Twin studies in human autoimmune diseases showing that indi- viduals with an identical genotype may be variably affected by dis- ease (concordance rates vary widely, from 15 to 50%, in identical twins with SLE or rheumatoid arthritis), demonstrating that en- vironmental insults and stochastic events likely play a significant role in the development of autoimmunity. Recent studies have also strongly implicated circumstances that generate neoantigens (e.g. somatic mutations in cancer) as important initiators of the specific immune response in some autoimmune diseases; this is discussed further next. In terms of potential environmental insults that may play a role in autoimmune disease, there is evidence of a role for infections, ir- radiation, and exposure to drugs and toxins. For example, exacerba- tions of SLE can follow sunlight

exposure, and there are numerous reports that disease initiation may have a similar association with ultraviolet irradiation in rare patients. Numerous infections have been postulated to play a role in disease initiation across the spec- trum of human autoimmune diseases. In rare cases, the association between antecedent infection and subsequent development of dis- ease is evident (e.g. coxsackievirus infection-induced autoimmune myocarditis, acute rheumatic fever following streptococcal infec- tion, Epstein–Barr virus infection, and childhood SLE). In most autoimmune diseases, however, it has not been possible to confirm such environmental connections with any certainty. This does not prove that a causal connection does not exist in these instances, but rather reflects several features of the diseases that greatly complicate the firm establishment of such a connection: • kinetic complexity of the autoimmune diseases—since develop- ment of autoimmunity occurs in several distinct phases, and once the propagation phase begins, establishment of a recognizable disease phenotype often takes months, evidence of the initiating insult may have disappeared by the time the environmental com- ponent is sought for the first time; • several different environmental insults may induce a similar response; • the environmental force may be extremely frequent in the popula- tion, but may only induce autoimmune disease in a unique subset of individuals with appropriate susceptibility genes. How various forces influence initiation of autoimmune diseases is not yet known for most autoimmune diseases, but several plausible mechanisms have been advanced. These include • the disruption of cell and tissue barriers, allowing previously se- questered antigens access to a previously ignorant immune system (see next); • inducing novel pathways of antigen presentation; • alteration of the structure of self-antigens; and • molecular mimicry. Some of these mechanisms are dealt with in more detail next. Pathogenesis Although extraordinarily complex in detail, the adaptive immune response operates by a set of relatively simple principles: (1) the immune system has the capacity to discern molecular structure in extremely fine detail; (2) it has a uniquely adapted set of signalling systems that computes the amount of antigen; (3) it responds in a binary way to contextual information, that is, seeing an antigen in the setting of a dangerous context (e.g. infection or cancer) initiates an immune response, whereas seeing the antigen in the absence of such costimulatory signals leads to tolerance. Numerous studies over the past two decades have underscored that the sustained autoimmune response is extremely similar to adaptive immune responses directed against foreign pathogens, except that the driving antigens in autoimmune disease are self-molecules. For example, autoantibodies in most autoimmune diseases display evi- dence of isotype switching (e.g. from IgM to IgG or IgA), and show features of having undergone affinity maturation through somatic hypermutation. These properties of autoantibodies require the ac- tivity of antigen-specific CD4+ T cells, and have therefore focused much attention on defining the mechanisms whereby self-reactive T cells are activated in autoimmunity. Since this is such a central issue in the understanding of autoimmunity, and since there are nu- merous mechanisms employed by the normal individual to prevent activation of autoreactive T cells, it is important to briefly review the mechanisms that the normal immune system uses to maintain toler- ance against self-proteins. Central and peripheral tolerance To prevent the survival of lymphocytes that will likely encounter their cognate antigens in healthy self-tissues, with potential auto- immune destruction of tissues, the immune system spends sig- nificant energy on testing the specificity of all receptors generated during antigen-independent development of lymphocytes initially in the thymus, and subsequently in the periphery. When the T-cell receptor generated through somatic recombin- ation recognizes a peptide–MHC complex in the thymus with high affinity/avidity, cells expressing this receptor are negatively selected (since they are likely self-reactive, and will recognize their cognate

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mechanism appears to involve the con- stitutive expression of Fas ligand in the relevant tissue (e.g. eye). When this molecule binds to and activates its receptor on lympho- cytes, these cells undergo apoptotic death, and are prevented from entering the tissue. Immunodominance and cryptic determinants Not all regions of a molecule are equally immunogenic. Regions of the molecule that are well-captured by class II MHC molecules during natural processing of self-antigens are able to tolerize T cells (these determinants have been termed ‘immunodominant’ by Sercarz and colleagues). In contrast, regions of self-molecules that are not gen- erated in significant amount during natural antigen processing (so- called ‘cryptic determinants’) cannot effectively tolerize T cells, since they are never seen by these cells either in the thymus or peripherally. This immunodominance appears to be influenced by the intrinsic affinity of the peptide for MHC class II, as well as by neighbouring structural determinants on the antigen that may influence its binding to the peptide-binding groove. On self-molecules, two sets of deter-minants can therefore be functionally defined (Fig. 4.6.1): • those that are easily processed and presented (comprising the dominant self), which readily tolerize developing T cells • those that are not presented in appreciable amounts after natural processing (comprising the cryptic self), which do not tolerize There are unusual circumstances in which processing of self- antigens may load different peptides into the groove of MHC class II than those generated during normal antigen processing. Examples include (i) somatic mutation of the autoantigen (e.g. in cancer), which might result in loading a unique peptide from that autoantigen which has not previously been seen and tolerized; (ii) mutation might also cause modified proteolysis of the autoantigen (creating or destroying a proteolytic cleavage site, which destroys the dominant epitope or generates a new dominant epitope); (iii) unusual proteolysis of an autoantigen prior to entry into the nat- ural processing pathway, allowing emergence of a previously cryptic epitope; (iv) high-affinity binding of the antigen to specific receptors or antibodies, which can hinder access of the dominant epitope to the antigen-binding groove of MHC class II molecules, or optimize the loading of a previously cryptic epitope. Since T cells recognizing these cryptic peptides have not previously been tolerized, such ‘autoreactive’ T cells can now be activated (Fig. 4.6.2).

(c) High affinity binding to another protein that alters processing • Antibody binds with high affinity to dominant epitope, and stops it from getting into the class II groove • The protein is cleaved with a different pattern to that normally observed during processing, and the
cryptic epitope is generated in amounts sufficient to load MHC class II • T cells have never seen this epitope before, and have therefore not been tolerized
• Autoreactive T-cell response initiated
MHC II Antibody/high affinity receptor The dominant epitope is preferentially loaded onto class II MHC during normal antigen processing Other regions are trimmed away, and are not presented in significant amount of MHC II processing Dominant Cryptic Ag processing No autoreactive T cells recognizing the dominant self exist in the host, because they have been tolerized MHC II (a) Normal processing of intact Ag self antigen (b) Generation of novel fragments Autoreactive T-cell response initiated • Dominant epitope destroyed
• Cryptic epitope loaded onto class II MHC • T cells specific for the cryptic epitope have never seen this self-antigen before, and are activated MHC II Ag processing Fig. 4.6.1 Dominant and cryptic T-cell epitopes in autoimmune disease. (a) The default processing pathway for intact antigen results in the preferential and reproducible loading of the ‘dominant’ peptide determinant into the antigen-binding groove of MHC class II. During establishment of thymic and peripheral tolerance, T cells

recognizing this dominant epitope are purged from the repertoire, but T cells recognizing cryptic epitopes do not encounter their antigens, and are not deleted or anergized. (b, c) When the processing of self-antigens is altered (e.g. by novel proteolysis or through high-affinity binding to another molecule), a different hierarchy of epitopes is loaded on to class II MHC. If cryptic epitopes are loaded in sufficient amounts, these peptides can stimulate autoreactive T-cell responses directed against the cryptic self, and drive the autoimmune process.

4.6 Autoimmunity 385 There are several clear demonstrations that autoreactive T cells recognizing cryptic epitopes can be activated in vivo through al- tered processing of self-molecules to reveal these previously immunocryptic epitopes. For instance, high-affinity binding of the HIV surface protein gp120 to CD4 alters the processing of CD4, and activates T cells which recognize epitopes of CD4 not generated during normal antigen processing. This mechanism may account for the autoimmune response to CD4 seen during HIV infection. Similarly, although intact mouse cytochrome c is not immunogenic in mice, cleavage of the molecule into smaller peptides induces a robust T-cell response to cryptic areas of cytochrome c, which were never previously presented by the natural processing pathway, and therefore did not induce tolerance. The revelation of cryptic epitopes in self-antigens is likely to be a highly relevant mechanism in many human autoimmune dis- eases, but the studies to demonstrate the importance of this mech- anism have only recently begun in earnest. Since the structure of autoantigens influences the hierarchy of dominant and cryptic and determinants generated when the molecule is processed, unique pro- cesses which alter the structure of molecules may play critical roles in initiation of autoimmune diseases. These unique events likely do not occur during normal homeostasis, but may occur preferentially during infectious or other proimmune events occurring at the host- environment interface. Relevant examples include: • Somatic mutation may create novel epitopes that bind with high affinity to the patient’s MHC class II alleles and effectively stimulate a CD4 T-cell response. Autoimmunity with damage to self-tissue can be driven when this immune response against the ‘mutanome’ also cross-reacts with the unmutated wild type autoantigens present in the patient’s tissues. Recent studies have demonstrated that this mechanism is relevant in patients with scleroderma, where mutations in a major scleroderma autoantigen (RNA polymerase 3) in patients’ cancers appear to initiate the immune response against that antigen. • Activation of unique proteolytic pathways that specifically alter the structure of autoantigens during immune effector pathways. It has recently been observed that most autoantigens targeted across the spectrum of human autoimmune diseases are specific- ally cleaved by granzyme B during killing of infected target cells by cytotoxic lymphocytes. This cleavage generates unique molecular fragments never generated in the organism during development or homeostasis. Interestingly, this cleavage is a unique feature of autoantigens, and does not affect nonautoantigens. Although it (a) Ag processing B T ‘Help’ Strong TH epitope T-cell epitope = Antibody = MHC II = TCR Processing TH X-reactive Self • Self-antigen release in setting of crossreactive activated B cell
• Revelation of cryptic self TH epitope Foreign Cryptic Foreign B Self B X-reactive Ab T Vs foreign ‘Help’ B T Autoreactive against cryptic epitope in self- antigen ‘Help’ Crossreactive Ab driven by self antigen B cell (b) Fig. 4.6.2 Molecular mimicry. (a) Foreign antigens, which clearly 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 response to the foreign antigen may generate a cross-reactive antibody response that also recognizes the self-protein. When the self-antigen is a cell-surface molecule, antibody-mediated effector pathways can lead to host tissue damage. Although the antibody response is cross-reactive with self-molecules, the T cells that drive

this response are directed exclusively at the foreign antigen. (b) Under highly novel conditions, the simultaneous liberation of significant amounts of self-antigen in the setting of a 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. These autoreactive T cells can now continue to drive an autoantibody response to the self-antigen. If continued release of self-antigen occurs as part of this process, a specific, adaptive immune response to self will be sustained.

 has been proposed that these cleavage events allow the efficient presentation of previously cryptic epitopes, this remains to be for- mally demonstrated. • Additional post-translational modifications that alter conform- ation of antigens, and modify their subsequent processing. It is noteworthy that numerous post-translational modifications of autoantigens occur, and that in some cases initiation of the auto- immune response is strictly dependent on the occurrence of these modifications. One of the most prominent examples is the post- translational deimination of arginine to citrulline in rheumatoid arthritis. Other examples include phosphorylation, acetylation, and isoaspartyl formation, among others. • Formation of high-affinity complexes between autoantigens and other viral or self-proteins. In all these examples, it should be remembered that the initiating event in autoimmunity requires that, on the background of appro- priate susceptibility genes, several stringent criteria needed to ini- tiate a primary immune response must be simultaneously satisfied. These include the generation of suprathreshold concentrations of self-molecules that have a structure not previously tolerized by the immune system, and the presentation of these unique molecular forms to T lymphocytes in the presence of costimulation (i.e. in a proimmune context). Molecular mimicry Foreign antigens, which clearly 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 response to the foreign antigen may generate a cross-reactive anti- body response that also recognizes the self-protein (molecular mim- icry). When the antigen is a cell-surface molecule, antibody-mediated effector pathways can lead to host tissue damage. Although the anti- body response is cross-reactive with self-molecules, the T cells that drive this response are directed at the foreign antigen (see following paragraphs). Diseases involving this sort of antigen mimicry there- fore tend to be self-limited. It is important to realize that molecular mimicry alone cannot explain self-sustaining autoimmune diseases, 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 pres- ence of the cross-reactive antibody response likely play critical roles in this regard (see next). Mechanistic insights into molecular mimicry Although several microbial and viral antigens have regions of high homology with various human autoantigens, a causal link between exposure to these foreign antigens and the onset or exacerbation of autoimmune disease has been extremely difficult to establish. There are, however, clear examples that suggest the existence of ‘one-shot’ autoimmune processes, in which cross-reactive antibodies directed against surface self-antigens are generated following infection, and result in tissue damage. This persists until infection is cleared, and the immune response wanes. Although the mechanistic details of this scheme are difficult to prove in vivo, several pertinent examples exist. One of these is a seasonal epidemic form of Guillain–Barré syndrome seen in northern China, which follows Campylobacter jejuni infection. Affected patients make antibodies recognizing gangliosides, and the disease has a self-limited course, which rarely recurs. The antiganglioside antibodies generated are likely respon- sible for the pathological findings of acute motor axonal neur- opathy. Another plausible example of this mechanism (although with meagre in

vivo evidence) is immune thrombocytopenia (ITP) in children. This process characteristically (1) follows an infectious process; (2) demonstrates antiplatelet antibodies, and (3) frequently shows durable remissions. The mechanistic details of this process have been difficult to prove in vivo, and cross-reactive epitopes on potentially initiating pathogens have not yet been defined. The single episodes of tissue damage in the setting of a cross- reactive immune response following infection must be contrasted to the sustained, autoamplifying disease frequently seen in other auto-immune syndromes. The central issues in this regard are (1) how T- cell tolerance to self-antigens might initially be broken, and (2) once this has occurred, why these antigens continue to drive the immune response to self. Examination of tolerance to cytochrome c, a ubi- quitous protein that has regions of homology and divergence across different species, has been very useful in understanding molecular mimicry of cross-reactive epitopes. Mouse cytochrome c shares sig-nificant homology with human cytochrome c, although the proteins are entirely different in other areas. When Mamula and colleagues used mouse cytochrome c to immunize mice, no T-cell or anti-body response to the murine protein was observed. When human cytochrome c was similarly used to immunize mice, strong T-cell epitopes on the foreign cytochrome c were able to induce a strong antibody response to the foreign protein. The antibodies induced recognized both the murine and the human forms of cytochrome c (i.e. cross-reactive antibodies that recognize the self-protein were produced). The T-cell response to cytochrome c was, however, dir- ected entirely against the foreign (human) form of the protein, and no T cells against the murine protein could be found. These cross- reactive antibodies disappear as the immune response to the foreign protein wanes. Interestingly, when mouse cytochrome c was included with human cytochrome c during the immunization, a T-cell response to human cytochrome c, and a humoral response to the human pro- tein that cross-reacts with the murine protein, was induced. Within a few days, a strong helper T-cell response specific for murine cyto- chrome c was detected. This breaking of T-cell tolerance to murine cytochrome c was dependent on activated B cells specific for cyto- chrome c, which likely exert their effect through altering the pro- cessing of mouse cytochrome c, potentially uncovering previously cryptic epitopes in the self-protein (see Fig. 4.6.2). In the presence of continued release of self-antigen, this response may become self- sustaining—self-antigen driving autoreactive T cells, providing help to autoantibody-producing B cells (Fig. 4.6.2). Molecular mimicry may therefore induce the production of cross-reactive antibodies, which, in the absence of liberation of sig- nificant amounts of self-antigen, should disappear when the for- eign pathogen is cleared. The form of epidemic motor axonopathy described here is likely representative of this scenario. Under highly novel conditions, the simultaneous liberation of significant amounts of self-antigen in the setting of a 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. 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 pro- cess. Understanding the mechanisms of ongoing antigen release at sites of tissue damage in autoimmune disease (e.g. unique pathways of cell injury and death) is a high priority for future work, as it pro- vides a novel target for therapy (see next). It is clear from the previous discussion that extraordinary com- plexity is operative in initiation of the human autoimmune diseases. The patient population is genetically heterogeneous, the human im- mune system is complex and extremely plastic, and it interacts with a plethora of environmental stimuli and stochastic events. The sim- ultaneous confluence of susceptibility factors and initiation forces to set off the self-

sustained and autoamplifying process is there- fore an extremely rare occurrence. In contrast, once activation of autoreactive T cells has occurred, the ability of the immune system to vigorously respond to vanishingly low concentrations of antigen, to amplify the specific effector response to those antigens, and to spread the response to additional antigens in that tissue, greatly re- duces the stringency that must be met to keep the process going (Fig. 4.6.3). Effector mechanisms in autoimmune diseases The initiation phase of autoimmunity requires cooperation be- tween many different cell types, including antigen-presenting cells, T cells and B cells, as well as numerous soluble mediators including antibodies, chemokines, and cytokines. The effector phase of autoimmunity uses the same immune and inflammatory effector mechanisms that the immune system has evolved for removing and destroying pathogens. These include activation of the com- plement cascade, which generates signals that effect inflammatory cell recruitment and activation. Similarly, ligation of activating Fc receptors on inflammatory cells by immune complexes activates macrophage and neutrophil effector function. Autoantibodies dir- ected against cell-surface antigens initiate antigen-dependent cel- lular cytotoxicity, likely mediated by macrophages and natural killer cells. Cytokines and chemokines play a central role in inflammatory cell recruitment and activation in the target tissue. Tissue damage can also be effected by cytolytic lymphocytes. The pathology char- acteristic of each autoimmune disease reflects both the particular antigens targeted, as well as the predominant effector mechanisms activated. One principle of central importance in the effector phase of auto- immunity is autoamplification, which appears to play a central role in the self-sustaining nature of the autoimmune process. Thus, im- mune effector pathways cause damage of cells in the target tissue, liberating antigen which further stimulates the immune response and effector pathways, thus liberating more antigen. Although this is likely an oversimplification, the view that the immune system plays a role in generating an ongoing supply of autoantigen is useful Environmental insult (e.g. viral infection) Antiviral immune response inflammation Clearance of infection repair of damage Normal Infected tissue Normal host Antiviral immune response Clearance of infection Generation of novel autoantigen structure Antiself immune response Infected tissue Autoimmune host Tissue damage Environment Susceptibility genes Initiation Propagation Fig. 4.6.3 Model of initiation and propagation of autoimmune disease. Autoimmune diseases are highly complex disorders, which require the simultaneous cooperation of multiple factors for their development. Numerous susceptibility genes (some of which regulate the immune response) appear to determine the threshold for disease initiation. In many diseases, a discrete, proimmune trigger (environmental or somatic mutation as occurs in cancer) likely plays a role in disease initiation, but is infrequently recognized. A critical requirement for disease initiation is the generation of suprathreshold concentrations of self-antigen with novel structure. Development of a recognizable disease phenotype generally requires marked antigen-driven amplification of the autoimmune response, in which immune effector pathways play a role in generating the ongoing supply of antigen to sustain the process.

 therapeutically, since it focuses attention on controlling both the supply of antigen as well as immune effector pathways (see next). Principles of amplification One of the central features of human autoimmunity is the tendency of the process to amplify progressively with the accumulation of significant immune-mediated tissue damage. Furthermore, in the vast majority of cases, once such amplification begins, the process is very unlikely to resolve spontaneously. Properties of autoantigens themselves may be very important in this phase, in terms both of acquisition of adjuvant properties, and of regulation of expression. The essential features of amplification are a substrate cycle, in which antigen expression and adjuvant

properties induce an immune re- sponse, which induces increased antigen expression and tissue damage—and further drive the immune response. The importance of tissue-specific autoantigen expression in focusing such immune responses is only beginning to be recognized. Acquisition of adjuvant properties by disease-specific autoantigens In recent years there have been dramatic advances in the under- standing of the mechanisms whereby specific molecules are selected as antigens in the various autoimmune syndromes. In spite of the fact that tens of thousands of molecules could be targeted by the immune system in autoimmunity, the number of molecules that are frequently targeted in the different phenotypes are markedly restricted—limited perhaps to a few hundred molecules at most. This has led to the proposal that frequently targeted autoantigens may themselves have properties that make them proimmune. This was first suggested by Plotz and colleagues. who observed that the autoantigenic histidyl aminoacyl-tRNA synthetase which is targeted in autoimmune myositis (but not non-auto-antigenic lysyl- and aspartyl-aminoacyl-tRNA synthetases) is chemoattractant to im- mature dendritic cells and other leucocytes. The authors suggested that the selection of a self-molecule as a target for an autoantibody response may be a consequence of proinflammatory properties of the molecule itself. They further suggested that modification of autoantigen structure during processes of cell damage or death may be critical in recruiting these additional functions of autoantigens. Toll-like receptors (TLRs) and other nucleic acid sensors One of the most likely receptor systems to sense and transduce the proinflammatory properties of autoantigens is the TLR family, which is the primary innate immune system transducer of pathogen- associated molecular patterns. Ligands for TLRs include both micro- bial and endogenous molecules, the latter group being particularly relevant to autoimmunity (see next). Microbial ligands include com- ponents of Gram-positive bacteria, Gram-negative bacteria, yeast, and protozoans. Although viral and bacterial nucleic acids are the most likely ligands for TLRs, accumulating data demonstrates that complexes containing endogenous nucleic acids are also able to signal through TLRs. Although the exact nature and source of endogenous ligands for TLRs in vivo remains unclear, recent studies have demon- strated that components from stressed, injured, and dying cells may play critical roles. Working in several models, numerous investigators have now provided evidence that the targeting of frequently targeted nucleoprotein autoantigens (which contain DNA or RNA) results from the ability of these nucleic acid components to ligate TLRs both in vitro and in vivo. For example, when TLR9-deficiency is bred on to MRL-lpr mice—which are an excellent model of SLE—animals no longer get autoantibody responses to chromatin. Similarly, when mice are rendered TLR7-deficient, the autoantibody response to Sm is markedly inhibited, and severity of the SLE phenotype is improved. These data confirm that autoantigens frequently selected in different autoimmune phenotypes likely have the dual property of being able to simultaneously activate the innate and adaptive immune systems, and that the ability to colligate TLRs plays a critical role. The like- lihood that the TLR-autoantigen interface will be therapeutically relevant in autoimmune processes is very high. Recent work has also underscored the importance of families of cytoplasmic nucleic acid sensors as targets of the immune response in autoimmunity, and as potential amplification hubs in tissue. These include MDA5, IFI-16 and alter autoantigens. One of the major pathways downstream of TLR ligation in auto- immunity appears to centre on a relatively rare class of immature den- dritic cells (plasmacytoid dendritic cells or pDCs), which can secrete large amounts of type I interferons upon TLR ligation, and which ex- press TLR7 and TLR9 at high levels. Ronnblom and colleagues have demonstrated that, when added to material from apoptotic or necrotic cells, autoantibodies from SLE and Sjögren’s syndrome patients with specificity for DNA or RNA autoantigens induce striking interferon secretion. Type I interferons have a broad set of functions which likely contribute to the

feed forward, propagation phase of systemic auto- immune diseases. For example, they (1) promote the differentiation of monocytes into mature DCs, which drive autoreactive T- and B-cell responses; (2) increase target cell sensitivity to killing pathways; (3) upregulate cytotoxic effector pathways; and (4) upregulate expres- sion of autoantigens. Targeting interferon pathways in systemic auto- immunity is currently a major focus for therapeutic intervention. Autoantigen expression in the target tissue in autoimmunity Another important component of the amplification cycle is the target tissue itself, and particularly the amounts and forms of autoantigens expressed at these sites. Unfortunately, very little is currently known about such parameters in vivo in relevant target tis- sues, in either normal or pathological circumstances. Insights from studies on human autoimmune myopathies and rheumatoid arthritis have begun to provide important insights into this problem. Thus, myositis-specific autoantigens are expressed at very low levels in normal muscle, but at high levels in myositis tissue, where antigen expression is at highest levels in regenerating muscle cells. Similarly, cells in synovial fluids from rheumatoid arthritis (RA) patients have very high levels of citrullinated protein antigens, apparently gener- ated by immune-mediated membranolytic pathways. These data sug- gest that enhanced autoantigen expression in the target tissue may be a feature of disease propagation, and that antigen expression during tissue damage or repair may provide an ongoing antigen source to sustain and amplify tissue damage. In this regard, the regulation of antigen expression (rather than exclusively pathways of immune-mediated damage) may have important therapeutic potential. Clinical features The clinical features of the different autoimmune diseases are ex- tremely diverse, and reflect the specific tissue dysfunction which

4.6 Autoimmunity 389 results from activity of immune effector pathways. Almost all tissues may be affected, including prominent involvement of endocrine or- gans, nervous system, eye, bone marrow elements, kidney, muscle, skin, liver, and gastrointestinal tract, blood vessels, lung, and joints. For tissue-specific autoimmune processes (e.g. type 1 diabetes, ITP, autoimmune haemolytic anaemia (AIHA)—see Table 4.6.1), symp- toms may relate to tissue hypofunction resulting from (1) target cell destruction (for type 1 diabetes, destruction of the β cells of the pancreatic islets; for ITP and AIHA, destruction and phagocytosis of platelets and erythrocytes); (2) antibody-mediated interference with function or downregulation of autoantigen expression (e.g. myasthenia gravis, bullous pemphigoid). In other cases, symptoms may arise from tissue hyperfunction (e.g. Graves' disease) due to activating effects of antibody binding (where antibodies to the TSH receptor induce nonphysiological secretion of thyroid hormone). In the case of systemic autoimmune processes (Table 4.6.2), symptoms frequently result both from localized target tissue de- struction (e.g. skeletal muscle in polymyositis, skin disease in SLE) as well as from the more general activities of inflammatory effector pathways. The latter result from (1) immune complex deposition Table 4.6.1 Autoantigens targeted in several tissue-specific autoimmune diseases Disease Tissue target Prominent autoantigen(s) Proposed disease mechanisms Clinical features Autoimmune haemolytic anaemia Erythrocyte surface Components of the Rh antigen, band 3.1, glycophorin, and several unidentified molecules Antibody-mediated destruction and clearance of erythrocytes Anaemia Autoimmune hepatitis Hepatocytes Smooth muscle cell cytoskeletal components Cytocshrome P450-2D6 ASGP-receptor Multiple Mild to severe chronic hepatic dysfunction in young women Epidemic Guillain– Barré syndrome
(N. China) Motor axons Axonal gangliosides Infection with Campylobacter jejuni induces cross-reactive antibody, which mediates axonal damage Acute autoimmune axonopathy Flaccid paralysis with areflexia Elevated cerebrospinal fluid protein Grave's disease Thyroid gland TSH receptor

Antibody-mediated stimulation of TSH receptor, leading to excessive thyroid hormone secretion Hyperthyroidism Goitre Grave’s ophthalmopathy Localized dermopathy Diabetes (type 1) β cells of the islets of Langerhans Glutamic acid decarboxylase (65-kDa form) Insulin Carboxypeptidase Cytotoxic lymphocyte-mediated destruction of islet cells Insulin deficiency and diabetes Idiopathic thrombocytopenia Platelet surface Platelet integrins Antibody-mediated platelet destruction and phagocytosis Thrombocytopenia, bleeding Inflammatory bowel disease Gastrointestinal tract Atypical p-ANCA ASCA Cytokine and lymphocyte-mediated epithelial damage and dysfunction Chronic intestinal inflammation marked by remission and relapse Multiple sclerosis Myelinated nerve fibres Myelin basic protein PLP MOG Transaldolase Activated cytokine pathways Activated effector lymphocytes Autoantibodies Demyelinating disorder primarily affecting young adults: protean clinical manifestations depending on location and size of classic plaques Myasthenia gravis Neuromuscular junction Nicotinic AChR Antibody-induced blockade and downregulation of AChR Striated muscle fatigue and weakness Myocarditis Myocardium Cardiac myosin Adenine nucleotide transporter Branched-chain ketodehydrogenase Infection with coxsackievirus induces myocardial damage and immunization with cardiac autoantigens Subacute congestive heart failure Pemphigus vulgaris Hemidesmosome junctions Desmoglein-3 Antibody-mediated disruption of epithelial cell junctions, with epidermal cell detachment Blistering skin lesions Psoriasis ADAMTSL5 Noncytotoxic CTL effects on melanocytes and keratinocytes Among the most frequent of T-cell-mediated
disorders with chronic, relapsing, hyperproliferative skin inflammation Rasmussen’s encephalitis Inhibitory neurons Type 3 glutamate receptor Antibody-mediated blockade of inhibitory neurotransmitter signalling Severe epileptic seizures, progressive degeneration of a single cerebral hemisphere Stiff man syndrome GABA-ergic neurons modulating spinal cord reflexes GAD67 Amphiphysin Blockade of inhibitory neurotransmitter signalling, possible autoantibody-mediated Rare disease characterized by severe, progressive stiffness with superimposed episodic muscle spasms, may be associated with autoimmune disease or malignancy Vitiligo Melanocytes Tyrosinase, TRP-1 Cytotoxic lymphocyte-mediated damage of melanocytes Skin depigmentation AChR acetylcholine receptor; ASCA, anti-Saccharomyces cerevisiae antibodies; MOG, myelin/oligodendrocyte glycoprotein; PLP, proteolipid protein.

390 SECTION 4 Immunological mechanisms at multiple sensitive sites (e.g. joints, kidney, skin, and blood vessel walls) with activation of the complement cascade and recruit- ment and activation of myelomonocytic cells; (2) ongoing secre- tion of proinflammatory cytokines. In this regard, the profoundly positive clinical effects of inhibitors of multiple cytokine pathways (including tumour necrosis factor (TNF), IL-6, IL12/23, IL-17) on the inflammatory symptoms and tissue destruction in rheumatoid arthritis and psoriasis underscore the central role of these general inflammatory mediators in generation and maintenance of the dis- ease phenotype in systemic autoimmune diseases. Prognosis Although the barriers that need to be overcome in terms of initiating an autoimmune disease are stringent and difficult to satisfy even in the setting of appropriate susceptibility genes, the immune system is equipped with a powerful memory. The mechanisms of this memory are still incompletely defined but include the generation of a population of memory cells specific for the antigen that initiated the response, which respond vigorously (both in terms of clonal ex- pansion, as well as effector function) to very low concentrations of antigen if they encounter it again. Since the autoimmune diseases are disorders driven by the ongoing release of self-antigen, this immunological memory con- stitutes a major barrier to complete cure. Autoimmune diseases therefore tend to be self-sustaining over long periods, and are often

punctuated by clinical exacerbations (flares), which are likely due to re-exposure of the primed immune system to antigen (e.g. SLE, autoimmune myositis, rheumatoid arthritis). The possibility of dis- ease recurring, even after long clinical remission, remains present in most of the autoimmune diseases. It is notable that early recognition of disease and early intervention may avoid the significant amplifica- tion of disease that renders the process so resistant to therapy. Early recognition is therefore a major goal for effective management. Tissue-specific autoimmune diseases may result in the complete destruction of the target tissue over time, with loss of function of that tissue accompanied by a waning immune response (e.g. type 1 dia- betes). Interestingly, in cases where immune-mediated tissue path- ology results from effector pathways being driven by a cross-reactive T-cell response to a foreign antigen (e.g. epidemic Guillain–Barré syndrome), disease has a finite duration, and generally does not recur. Therapy It is not possible to discuss the therapy of this broad group of dis- orders in any detail in this chapter, but a few principles that underlie current approaches to therapy are discussed. Autoimmune diseases cause significant tissue dysfunction through (1) inflammation, (2) tissue destruction with loss of functional units, (3) the conse- quences of healing, and (4) functional disturbances (e.g. interference with acetylcholine signalling by autoantibody to the acetylcholine receptor and inducing receptor downmodulation in myasthenia Table 4.6.2 Systemic autoimmune diseases Disease Prominent tissue target Prominent autoantigen(s) Proposed disease mechanisms Clinical features PM/DM Skeletal muscle Mi-2 helicase Aminoacyl-tRNA synthetases DNA repair machinery Complement activation (DM) Activated effector lymphocytes (PM) Proximal muscle weakness (PM/DM) Heliotrope/skin rash (DM) Interstitial lung disease Rheumatoid arthritis Synovial joints IgG Fc Citrullinated peptides (CCP) Citrullinated vimentin, fibrin, calpastatin Peptidyl arginine-deiminase (PAD)-4 Activated cytokine pathways (TNF) Activated effector lymphocytes Immune complex deposition Symmetric, erosive polyarthritis Scleroderma Skin, lung, GI, kidney, heart Topoisomerase-1 (diffuse form) RNA polymerases (diffuse) Centromere proteins (CREST form) Blood vessel damage by activated effector lymphocytes and autoantibodies Progressive fibrosis of skin, and multiple internal organs (including GI, lung, kidney, and heart) Raynaud’s phenomenon Vasculopathy Sjögren’s syndrome Exocrine glandular epithelial tissue Ro/SS-A; La/SS-B Epithelial cell death induced by cytotoxic lymphocytes and other immune effector pathways Keratoconjunctivitis sicca Systemic lupus erythematosus Numerous, including skin, kidney, joints, haematologic elements, nervous system dsDNA/nucleosomes Splicing ribonucleoproteins (e.g. Sm, U1-RNP) Ro/SS-A; La/SS-B Ribosomal P proteins Phospholipid-protein complexes Cell death/abnormal clearance of apoptotic cells Nucleoprotein complex ligation of TLRs inducing prominent interferon secretion Autoantibody-mediated pathology Immune complex deposition Multisystem inflammatory disease Skin lesions Arthritis Renal disease Anaemia, thrombocytopenia Granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis) Numerous, including upper airways, lungs, kidneys, and skin Neutrophil proteinase-3 (c-ANCA) c-ANCA binding to neutrophil surface induces degranulation in the vessel wall with consequent damage Multisystem inflammatory vascular disease with predominance of sinuses, middle ear, lung, and renal involvement DM, dermatomyositis; GI, gastrointestinal; PM, polymyositis.

 gravis). Therapeutic interventions in autoimmune diseases are gen- erally focused on controlling immune and inflammatory pathways, and at replacing or accommodating lost function. Control of immune and inflammatory pathways responsible for ongoing damage Since in most instances the critical autoantigens and effector path- ways responsible for disease have not been fully defined, this goal is frequently extremely challenging. Thus, frequent use is made of anti-inflammatory and immunosuppressive therapies which broadly target many aspects of the immune response (e.g. steroids, azathioprine, cyclophosphamide, methotrexate, mycophenolate).

Since a robust immune response is required to protect the host from a myriad of infectious threats, this nontargeted suppression of the immune system can have deleterious consequences in terms of in- creased susceptibility to infection, with its attendant high morbidity and mortality. The hazards of nontargeted immune suppression makes thera- peutic targeting of specific inflammatory pathways extremely at- tractive, and there are recent examples in which this approach has been highly successful. In many patients with rheumatoid arthritis, the maintenance of chronic inflammatory joint pathology appears to be dependent on the activity of several cytokines. Specific inhib- ition of TNF, IL-6, IL-17 through the use of either soluble receptors or humanized monoclonal antibodies has led to an astonishing ef- fect on disease activity in various inflammatory arthritides, with abolition of systemic symptoms and a striking decrease in the rate of joint destruction. These positive effects were associated with only a minimal increase in susceptibility to infection, although this risk is certainly present. These therapies also served as a model demonstrating that the use of injectable forms of biological ther- apies (monoclonal antibodies or receptors) as therapeutic agents in the general population was feasible. The potential that early diagnosis and specific intervention may have a higher chance of reversing the process if this occurs before the immune response amplifies and spreads to multiple antigens remains tantalizing, and early observations in RA and cancer- associated autoimmunity are hopeful in this regard. As noted here, modulation of additional immune effector pathways, TLR or cytoplasmic nucleic acid sensor signalling, or autoantigen expression in the target tissue are also important targets for novel therapy in the autoimmune diseases. Another example of specific targeting of proinflammatory path- ways is that of intravenous immunoglobulin (IVIG). This is prepared from pooled serum and its major component is immunoglobulin G (IgG). IVIG therapy has been used as a treatment of several auto- immune diseases, including ITP, autoimmune myositis, and acute demyelinating polyneuropathy, but is only available at prohibitive cost. Recent data from mice has demonstrated that IVIG induces surface expression of the inhibitory Fcγ receptor (Fcγ RIIB) on macrophages, and shifts the balance of signalling through Fc re- ceptors towards inhibition, down regulating the proinflammatory response to immune complexes. It is likely that continued iden- tification of additional agents that precisely modulate specific inflammatory pathways will have a major therapeutic impact on this group of diseases. Interventions aimed at replacing or accommodating lost function Most autoimmune diseases are associated with loss of function of organs and tissues, many of which perform essential physiological functions. Indeed, recognition of the autoimmune phenotype in many instances requires that tissue damage is sufficiently severe to have led to characteristic loss of function. For example, loss of insulin-secreting β cells of the pancreatic islets results in type 1 diabetes, and blockade and downregulation of the nicotinic acetyl- choline receptor causes striated muscle weakness and fatigue in my- asthenia gravis. Similarly, chronic immune complex deposition in glomeruli causes renal inflammation and scarring in SLE. Where significant functional reserve is still present in a particular dis- ease, a strong argument can be made for preventing further damage through specific or general immunosuppressive strategies described here. This is particularly relevant where the ‘supply’ of tissue that could be damaged is essentially inexhaustible (e.g. most instances of systemic autoimmune disease). Where functional impairment is already established, interventions aimed at replacing or accommo- dating lost function are indicated. For example, insulin replacement is required for type 1 diabetes, and treatment for hyperthyroidism is indicated in Graves’ disease. FURTHER READING Banchereau J, Pascual V (2006). Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity, 25, 383–92. Cho JH, Feldman M (2015). Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies. Nat Med, 21, 730–8. Feldmann M, Maini RN (2001). Anti-TNF alpha therapy of

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