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REVIEW ARTICLE

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Animal models of autoimmune diseases

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Abstract Failure of distinction between self and non-self is regarded a critical event in the pathogenesis of several human diseases such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, uveoretinitis or diabetes mellitus. Autoagressive immune reactions driven by activated autoreactive lymphocytes are a characteristic feature of these autoimmune diseases. The mechanisms by which the pathogenic control of autoreactive lymphocytes deviates from physiology can be studied in appropriate animal models under well-defined experimental conditions. Experimental models of autoimmune diseases in rodent inbred strains allow for the genetic mapping of susceptibility loci and might help to identify candidate genes also relevant to the pathogenesis of human diseases. Finally, the experimental models are valuable tools to develop rational immunotherapeutic strategies. Interesting features of some of the models employed for such research will be introduced in this review.

Key words Autoimmune diseases · Pathogenesis · Animal models

Introduction

Autoimmune diseases are believed to be caused by an underlying failure of the immune system to distinguish self from non-self. Such distinction, however, is not absolute but is relative, since external factors, within the context in which a given antigenic structure is presented, greatly shape the outcome of self/non-self distinction. The immune system, in addition, is equipped with a broad spectrum of different mechanisms to respond to antigenic challenges. The very diversity in the receptor and response repertoire, conceivably evolved to combat the greatest variety of infections and to maintain broad self tolerance in health, may, on the other hand, be reflected in a variety of pathogenic mechanisms leading to different autoimmune diseases. This complexity and its possible aberrations in autoaggressive disorders have to be considered most closely when devising therapeutic means aimed at restoring self tolerance.

Lymphocytes define what is self and non-self in a given environment. During their differentiation in the bone marrow and thymus, they receive receptor-mediated positive signals from self structures in order to become positively selected. Since in this phase a certain degree of self recognition may represent a survival factor, it is not surprising to find lymphocytes in the periphery that are equipped with both the ability to recognize, and the potential to respond to self structures. In physiological conditions, thus, there exist lymphocytes with autoreactive potential, as well as several structural requirements for the development of autoimmune disorders. Normally, however, the autoreactive lymphocytes are not harmful; therefore, a number of protective mechanisms must restrain autoreactivity from becoming adverse autoaggressiveness. Some of these mechanisms have been recently clarified: (a) deletion of lymphocytes carring high-affinity receptors for abundant self proteins by an active suicide mechanism (apoptosis); (b) induction of functional deviation in response to a challenge that does not provide complete support to trigger full activation; such inappropriate stimuli lead immunocompetent cells to functional deficits (anergy) or deviation in their cytokine response; (c) development of active suppression by a special subset of lymphocytes that have experienced contact with self antigens or anti-self lymphocytes; (d) ignorance of potentially autoreactive lymphocytes that fail to become activated by self antigens either because

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these are relatively hidden in the tissues or because of inappropriate presentation by MHC molecules.

The immune system takes advantage of all these principles to control self recognition. Autoimmune diseases develop as pathogenic exceptions to these rules. The way in which the pathogenic control mechanisms deviate from physiology, however, may differ considerably among different autoimmune diseases. Animal models of autoimmunity are very useful to study diverse immunopathogenetic processes in well-defined experimental conditions, and help thereby to develop rational immunotherapeutic strategies. Interesting features of some of the models employed for such research will be, therefore, introduced.

Lymphocyte differentiation defects: murine systemic lupus erythematosus

A number of genetically defective mouse strains spontaneously develop a systemic disorder that resembles in many aspects human systemic lupus erythematosus (SLE) [1]. Examples of such defects are the Fas antigen and Fas receptor mutations, which cause defective apoptosis during lymphocyte maturation [2]. The genetic defect interferes with the peripheral deletion ot T lymphocytes [3] resulting in excessive lymphoproliferation that is associated with enhanced cytokine release and overproduction of circulating immunoglobulins. Organ inflammatory disorders occur as a manifestation of the systemic disease, for example, autoimmune sialadenitis resembling Sjögren's syndrome [4] or chronic arthritis resembling rheumatoid arthritis (RA) [5]; a fatal form of progressive glomerulonephritis also develops as a consequence of precipitating immune complexes. A similar syndrome is described in the NZB/W mouse, possible associated with a basic B-cell differentiation defect [6], as well as in the BXSB mouse, which exhibits enhanced antibody production to the retroviral antigen gp 70, caused in turn by a defective Y-linked gene [7].

Thus, the complex phenotype of organ autoimmunity in different lupus models is associated with different molecular defects that share the feature of affecting lymphocyte differentiation. However, the complex cascade of events in the pathogenesis of lupus models is unlikely to represent chronological steps resulting from a single genetic defect [8]. One must also consider that genetic factors unrelated to apoptosis genes have a considerable impact on disease susceptibility and clinical phenotype in different inbred strains of autoimmunity-prone rodents; this genetic make-up may critically affect, among other factors, cytokine regulation. For instance, a tumor necrosis factor alpha (TNF-α) allele associated with low TNF-α production due to mutations in the 3′ untranslated region [9] correlates with the pathogenesis of lupus nephritis in (NZB×NZW) F1 hybrid mice [10]. Recent genetic analysis on a whole genome scale has enabled the chromosome localization of almost 40 gene loci that predispose to autoimmunity in animal models [recent review: 11). Nine identified loci (in addition to the lpr/Fas and gld/Fas ligand loci [12]) are associated with murine SLE [review: 13]. Nonetheless, each of these loci still spans a considerable distance on the respective chromosome. Ongoing mapping in murine SLE will allow, in the near future, the identification of all susceptibility genes involved and hence add to our understanding of the complex mechanisms underlying systemic autoimmune diseases.

Infectious diseases and autoimmunity

Infectious agents can cause chronic inflammatory diseases sustained by autoimmune processes. The activation of autoreactive lymphocytes can occur in response to viable parasites or to persistent parasite antigens. The Theiler-virus-induced encephalomyelitis, for example, develops in certain mouse and rat strains in the form of an autoimmune inflammation that can be transferred to naive syngeneic animals with donor T cells [14]. In septic arthritis caused by certain arthritogenic *Staphylococcus aureus* strains in mice, in turn, the secretion of the superantigenic endotoxin TSST1 leads to expansion of Vβ11-expressing T cells in the joints. Accordingly, specific blockade of the T-cell receptor (TCR)-Vβ11 blocks the development of arthritis [15].

A severe T-cell-dependent chronic polyarthritis can be induced in rats by injection of bacterial cell wall fragments [16–18]. The pathogenesis of the disease seems to be mediated by the prolonged activation of macrophages, which attempt to phagocytose the hardly digestible bacterial cell wall fragments spread in the reticulo-endothelial system [16, 17]. Such a process also affects the macrophage populations in the joint as an essential part of the reticulo-endothelial system. Closely related to this type of pathogenesis is the mycobacteria/adjuvant-induced arthritis model in the rat, in which the spreading of antigenic fragments induces chronic synovitis, as well as systemic granulomas [19]. Therefore, in diseases characterized by the persistence of parasite fragments or live infectious agents, chronic autoimmunity can be maintained in different ways, such as superantigen activation of T cells, cross-reactive immune responses or the presence of adjuvant material enhancing autoantigen presentation.

Organ- and tissue-specific autoimmune diseases

Typical organ-specific autoimmune diseases are characterized by autoimmune responses towards a limited set of immunodominant epitopes present on antigens that exclusively reside in the target organ.

Experimental autoimmune uveoretinitis

A typical case in the animal is experimental autoimmune uveoretinitis (EAU), which is induced by immunization

with some retinal photoreceptor-specific antigens, i. e. the interphotoreceptor retinoid binding protein (IRBP), a 130- to 140-kD glycoprotein representing a major component of the interphotoreceptor matrix [review: 20], or the S-antigen, a 48-kD protein of the rod outer fragment [21, 22]. EAU is characteristically associated with lymphocytic infiltrations of the corpus pineale in which the retinal antigens are also consistently expressed, with a common phylogenetic origin of the retina and the pineal gland from photoreceptors. In several animal species and/or strains [review: 23], activation of autoreactive B and T cells leads to inflammation of the retina, characterized by prominent polymorphonuclear (PMN) infiltration. The adoptive transfer of the disease by means of $CD4^+$/MHC-II-restricted T-cell lines [24, 25] indicates a crucial role of T-cell-derived chemotactic cytokines mediating PMN recruitment, whereas humoral responses seem to scarcely participate in the pathology. The scenario that finally leads to retinal damage seems to involve the following cascade [23]: initial random extravasation of sensitized T helper cells, predominantly of the Th1 type [25, 26]; IFN-γ-induced expression of MHC-II molecules on retinal pigment epithelial cells and at the blood-retinal interface; in situ presentation of endogenous retinal antigen by $MHC\text{-}II^+$ cells, resulting, in concert with a facilitated interaction of adhesion molecule (for example, upregulation of ICAM-1), in the expansion of sensitized lymphocytes. The secretion of lymphokines attracts PMN, monocytes and mast cells; these, upon release of their own mediators, lead to permeabilization of the blood-retinal barrier, provoking further recruitment of inflammatory cells. The actual damage to the photoreceptors can be produced by several factors, involving oxygen radicals [27].

The EAU model of organ-specific autoimmunity is of particular interest since it was long believed to result from a special anatomical condition in the eye, such as the lack of lymphatic drainage, which maintained the immune system ignorant of the existence of intraocular antigens. However, rather than being sequestered in a hidden compartment, the antigens are released into the blood circulation via Schlemm's canals, where they, in fact, elicit a systemic, active deviant immune response {"anterior chamber-associated immune deviation (ACADI)", [28]}. Although the entire cascade of events that is involved in the maintainance of this immunoinhibitory condition remains to be elucidated, the presence of high concentrations of transforming growth factor beta (TGF-β) in normal aqueous humour clearly contributes to the deviant form of systemic autoimmunity towards eye antigens [29]. In addition, retinal pigment epithelial cells can express an inducible form of nitric oxide (NO) synthetase that may produce locally high concentrations of NO. Since NO has cytostatic and cytotoxic properties, it may play an important role as an inducible immunosuppressant within the microenvironment of the eye at the site of lymphocyte activation [30, 31].

Spontaneous insulin-dependent diabetes mellitus

Insulin-dependent diabetes mellitus (IDDM) appears a far more complex situation, as the activity of autoreactive T and B cells is directed towards many different epitopes [32, 33]. In NOD mice, which spontaneously develop IDDM, the initial autoimmune response is confined to a limited set of epitopes of glutamic acid decarboxylase (GAD), of which two isoforms exist (GAD65 and GAD67). Preclinical stages of the disease are associated with periinsulitis (weeks 4–6), whereas overt diabetes develops as beta islets are progressively destroyed (weeks 18–20). Initially, macrophages, dendritic cells, and B and T lymphocytes accumulate in the periductal areas outside the islets. Progressively, minimal histological signs of islet inflammation (intra-insulitis) become apparent, being associated and most likely mediated by reactivity against GAD [34, 35]. At later time points, the T-cell response undergoes a clear diversification, spreading to additional determinants of the GAD molecule, as well as to insulin [36]; the response also spreads to the heat shock protein HSP60, whose expression is not restricted to pancreatic β cells [37]. Indeed, not only does treatment of NOD mice with HSP60 prevent the development of IDDM [38], but a HSP60-specific peptide can also re-establish euglycaemia in the established phase of the disease [39]. Studies with NOD mice deficient either in MHC-I or MHC-II, and in turn devoid of $CD8^+$ and $CD4^+$ T cells, respectively, have clearly shown that both T-cell subsets are essential for islet destruction [40, 41]. Although the respective contribution of these T-cell subtypes remains to be elucidated, a proposed scenario is that $CD8^+$ T cells initiate β-cell injury, whereas $CD4^+$ T cells subsequently amplify the response [41]. Also, the $CD4^+$ population is far more effective in adoptive transfer experiments of IDDM, probably through production of cytokines [for example interferon gamma (IFN-γ) and TNF] that exert direct pathogenic effects within the islets.

The importance of the cytokine milieu for IDDM (although the same applies to other models of autoimmunity) is underlined by the observation that administration of cytokines that promote Th1 differentiation exacerbates the disease, whereas monoclonal antibodies that specifically block Th1-derived cytokines are protective [42]. Administration of interleukin-4 (IL-4) [43] or IL-10 [44], both of which promote Th2 development, appears to protect NOD mice from diabetes. However, to explain the complex immunoregulation in IDDM strictly in terms of a Th1/Th2 concept may be an oversimplification. Experimental data show, in fact, that $CD4^+$ Th1 autoreactive T-cell clones derived from NOD mice suppress the adoptive transfer of diabetes [45]. Further support for a higher degree of complexity derives from the demonstration that T cells expressing a diabetogenic TCR, and cultured under conditions that promote Th2 development, fail to mediate protection in NOD recipients [46].

In general, the particular distribution of target structures in different models points to a crucial condition that seems to predispose to the development of autoimmune disorders, that is, the restricted availability of antigens as organ-spe-

cific gene products. After the onset of autoimmune attacks, the target organ is usually severely damaged or destroyed, resulting, on the one hand, in functional deficits and, on the other, in regression of the inflammatory component due to exhaustion of the autoantigens.

Closely related to organ-specific pathologies are tissue-specific autoimmune diseases. In these disorders, the target structures are abundant, but restricted in a tissue-specific fashion. The abundance of the target may prevent the rapid destruction of the tissue and lead to persistence of inflammation in a chronic fashion. Chronicity, on the other hand, may be favoured by the fact that the affected tissues are not completely exposed to the immune system.

Experimental allergic encephalomyelitis

Experimental allergic encephalomyelitis (EAE), a murine model with histopathological and clinical similarities to the relapsing-remitting and chronic-progressive forms of human multiple sclerosis (MS), is probably the best characterized example of a tissue-specific autoimmune disease, the myelin in the central nervous system (CNS) being the target of the inflammatory processes. Due to the far-reaching importantce of EAE, very often used for devising and testing new experimental designs, this model is therefore reviewed with some detail.

EAE is characterized clinically by ascending paralyses of the hind limbs and histologically by perivascular infiltration of mononuclear cells, as well as deposition of fibrin adjacent to areas of actue and chronic demyelination in the brain and spinal cord [47]. The inflammatory process in the CNS is driven by an autoimmune response to myelin proteins. The crucial importance of T-cell-mediated autoimmunity to neuroantigens is documented by the observation that myelin basic protein (MBP)-specific T cells adoptively transfer disease [48, 49]. The production of pro-inflammatory cytokines by MBP-specific Th1 cells appears to result in CNS damage via chemoattraction and activation of monocytes and macrophages, which, in turn, mediate the terminal non-specific pathways of tissue destruction [review: 50]. B cells may also contribute to a coordinated autoimmune attack, since complement depletion in the mouse [51] or neonatal depletion of B cells in the rat by anti-μ treatment [52] render animals resistant to EAE. After intradermal immunization with MBP, the complex of neuroantigens and their accompanying potent adjuvant are transported to the draining lymph nodes in the periphery, creating a reservoir of autoantigenic determinants that may activate effector T cells and fuel a chronic inflammatory process [53]. Upon activation, the sensitized lymphocytes leave the lymphoid system and reach their target organ via the circulation. The activation state, by virtue of expression of adhesion molecules, allows entry through the blood-brain barrier, which is formed by specialized capillary endothelial cells connected through tight junctions. Several adhesion molecules may be involved in the process, such as the α4-integrin VLA-4 (CD49d/CD29), or members of the immunoglobulin superfamily, such as CD2, which bind to adhesion molecules on the inflamed endothelium, for example VCAM-1 (CD106) or LFA-3 (CD58), in the first step of diapedesis. Accordingly, blockade of VLA-4 interactions reverses clinical paralysis in acute EAE and prevents relapses in chronic EAE [54, 55]. Following extravasation, T cells still have to pass through the basement membrane barrier to gain access to the white matter surrounding the axons. Matrix metalloproteinases (MMP) gelatinase A and B may be critical for the degradation of the extracellular matrix molecules of the basement membrane, and are very likely to be involved in leucodiapedesis of the blood-brain barrier. Indeed, there is gelatinase B immunoreactivity in MS lesions [56], and treatment with the MMP inhibitor hydroxamic acid reverses EAE manifestations and prevents relapses mainly by restoring the damaged blood-brain barrier [57]. Once the immunocompetent cells have spread to the white matter, a coordinated attack is initiated, involving release of pro-inflammatory cytokines, immunoglobulin-mediated complement lysis and myelin attack by activated macrophages.

While classic studies have clearly documented the immunogenic potential of spinal cord homogenates [58, 59], MBP [60] or proteolipid protein (PLP) [61], research has recently focused on several synthetic peptides corresponding to the major encephalitogenic regions of these proteins, which include MBP 1–9 and MBP 89–101 [62–64], or the peptides PLP 43–64 [65], PLP 56–70 [66], PLP 103–116 [67], PLP 139–151 [68], and PLP 178–191 [69]. Notably, these peptides differ in their capacity to induce acute or chronic forms of EAE; their ability to induce EAE in various mouse strains, in turn, mainly depends on how the particular peptide sequence binds to different MHC-II molecules [70]. The disease manifestations can very between an acute form with a short-duration paralysis 9–14 days after immunization, or a chronic relapsing course (CR-EAE), in which severe relapses superimpose on a background of continuous progression.

Most MBP-derived peptides (for example MBP 1–9) induce only the acute form of EAE, with no relapses or further progression. This acute flare provides, therefore, interesting insights into control mechanisms that downregulate autoimmune responses to neuroantigens and impede the shift into chronicity. The acetylated aminoterminal MBP peptide (MBPAc 1–9) is recognized by encephalitogenic T cells that predominantly use the TCR Vβ 8.2 gene segment. When mice recover from acute EAE, peripheral $CD4^+$ T cells expand in response to a single immunodominant TCR peptide from the Vβ 8.2 chain (amino acids 76–101), indicating natural priming during the initial phase. Cloned T cells, specific for this TCR peptide, specifically suppress proliferative responses to MBPAc 1–9 in vivo and protect mice from MBP-induced EAE. Thus, MBP immunization elicits both disease-causing and disease-regulatory, peptide-specific $CD4^+$ T cells [71]. In acute models of EAE, recovery from the first episode is also associated with resistance to re-induction of disease. Regulatory cells of the $CD8^+$ T-cell subset seem the main participants in this form of resistance [72, 73]. From these

observations, it appears that failure or disruption in establishing sufficient antigen-specific regulatory networks may predispose to repetition of autoimmune attacks and chronicity. Active suppression, on the other hand, can be overcome under certain circumstances, for example through non-specific activation of MBP 1–11 reactive T cells by the superantigen staphylococcus enterotoxin B (SEB); this interference can break the resistance acquired during the first episode, provoking a paralytic relapse in mice that had otherwise fully recovered from self-limiting form of EAE [74].

Some MBP peptides, on the other hand, induce exclusively the chronic-relapsing form of EAE. PLP 43–64, for example, provokes CR-EAE in PL/J mice [49], PLP 139–151 induces relapses in SJL mice [75] and the MBP 89–101 peptide leads to chronic EAE in B10.RIII (H2r) mice [76]. Although in chronic MBP-induced EAE the autoimmune response is usually directed towards one particular immunodominant peptide, this selectivity can shift during the course of the disease, due to the coexistence of suppressor and trigger mechanisms that differentially affect distinct neuroantigen-specific T cells. Such "spreading" of T-cell determinants is not restricted to MBP-induced EAE, but is also described in peptide-induced CR-EAE [77, 78]. In contrast to the acute form of EAE induced by the MBP 1–9 peptide, the TCR repertoire involved in CR-EAE is rather diverse, with no preferential V gene usage [79]. Thus, chronicity in CR-EAE can be referred at least to two phenomena, the spreading of antigenic determinants and the diversity of the TCR repertoire; these mechanisms bear important implications for antigen-specific approaches to treat chronic autoimmune diseases. The theoretical advantage of antigen-specific immunomodulatory therapies to selectively block adverse immune reactions fights the notion that even if the primary autoantigen of the disease should be known, the spreading of autoimmunity to secondary determinants during chronicity limits the applicability, if at all, to newly diagnosed patients. The knowledge that determinant spreading may follow predictable rules of hierarchy [80], on the other hand, may greatly simplify this problem. In EAE, the predictability of the spreading cascade and its invariant relationship to the occurrence of relapses have been exploited to achieve epitope-specific blockade of the progression of the disease into a chronic phase [77, 80]. Accordingly, the systemic administration of high doses of spreading encephalitogenic peptides (but not that of non-spreading encephalitogenic peptides) arrests the further progression of established EAE [80]. This successful interference with the spreading cascade demonstrates that autoimmune diseases might represent highly structured deviations from the tolerant state and should encourage further attempts at epitope-specific intervention in chronic autoimmune diseases.

Collagen II induced arthritis

Collagen-II arthritis (CIA) is an animal model for RA, and represents a second example of tissue-specific autoimmunity. T and B cells with specificity for collagen II (CII) are present in the joints of RA patients [81, 82], indicating that CII could be a potential autoantigen in RA. The CIA model, developed in the rat [83] and later in mice [84], is induced by immunization with CII emulsified in complete Freund's adjuvant; after 3 weeks the animals develop the first clinical signs, with joint swelling and oedema. Of note, the clinical course of the disease is crucially dependent on whether autologous or heterologous collagen is used for disease induction. While the heterologous-induced arthritis is characterized by active joint erosion during a severe but self-limited disease, CIA induced by autologous CII leads to cartilage erosions in a chronic course [85]. As most extensively studied in mice, the development of CIA is strongly associated with certain MHC-II haplotypes [86, 87], indicating that the model is dependent on T-cell recognition of a restricted set of CII peptides presented by appropriate MHC molecules [88]. However, proteins in cartilage are physiologically more exposed to the immune system than, for example, myelin proteins in the CNS; this may bear critical consequences for the degree of tolerance that may be endowed in lymphocyte subpopulations. Indeed, autoreactive T cells specific for CII are not easily activated in vivo, although they can be maintained in T-cell lines in vitro and can adoptively transfer a subclinical form of the disease [89]. In addition, CII-specific autoreactive T cells require larger amounts of antigen to proliferate in vitro than heteroreactive T cells [90]. Immunization of mice with heterologous (rat) CII preferentially leads to activation of heteroreactive T cells that do not cross-react with autologous CII [91]. In contrast to CIA, in the case of EAE, MBP-autoreactive T cells can easily be activated in vivo, remaining suitable for clonal expansion in vitro and for transferral of severe and/or chronic forms of disease [92]. Thus, autoreactive CII-specific T cells seem to be in a partially tolerized state, a condition that may account for differences in the clinical manifestation of CIA elicited by heterologous or autologous CII. In spite of their poor proliferation in response to collagen, these cells nonetheless retain important effector functions, such as IFN-γ production and B-cell help; these functions may still allow these partially anergized cells to mediate CIA [93].

T-cell recognition of proteolytically processed CII critically requires that CII is in its native conformation, that is, the intact triple helical structure [83, 94]. The conformation requirements, as well as the dependency on functional B cells [95, 96], indicate that autoreactive CII-specific B cells are crucial to the pathogenesis of CIA. In high responder mice, such as DBA/1 (H2-q), for example, there is an apparent lack of negative selection of CII autoreactive B cells. As a consequence, immunization of DBA/1 mice with heterologous CII gives rise to early activation (days 5–9 post-immunization) of IgG-secreting autoreactive B cells; these recognize a set of immunodominant native structures on the triple helical moiety of the autologous CII molecule [89, 95]. The autoantibodies are cross-reactive with CII from various species (i.e. human, chicken, bovine), but, within the same species, they do not cross-react with any of the systemically available colla-

gens, for example type I (CI), despite a homology of 80% at the amino acid level, suggesting that CI-reactive B cells might have been negatively selected. The pathogenic potential of CII-specific autoantibodies, in turn, is indicated by the observation that, after intraperitoneal injection into syngeneic mice, they bind to articular cartilage [96] and induce synovial inflammation and even erosive arthritis [97].

The immunoglobulin secreting plasma cells apparently dominate the acute phase of arthritis. The autoantibodies bind to cartilage and lead to Fc-mediated complement activation, chemotactically recruiting inflammatory cells to the joint compartment; it is also possible that immunoglobulin binding to FC receptors triggers inflammatory cells to release digestive enzymes that directly mediate cartilage destruction. The importance of the complement-dependent pathway is demonstrated by the observation that CIA-susceptible mouse strains produce high levels of complement-fixing IgG2a and IgG2b isotypes in response to immunization with CII [98] and that complement-depleted mice are resistant to CIA induction [99].

B cells may also be important in the later response to CII, for example in connection with epitope spreading in T-cell reactivity, since the bound antibodies, via protection of the antigenic determinants, may modulate the antigen processing and thereby the selection of peptides that are presented by antigen-presenting cells [100]. The crucial role of cognate interactions of T and B cells in CIA is also underlined by the protective effect of treatment with anti-gp39 antibodies, which interferes with the CD40-CD40 ligand interaction [101].

Experimental autoimmune myasthenia gravis

In experimental autoimmune myasthenia gravis (EAMG), the autoimmune response is directed towards the acetylcholine receptor (AChR), leading to destruction of the receptor and to clinical signs of muscular weakness. The human disease is associated with follicular hyperplasia of the thymus, or even thymomas, in a high percentage of patients. Although the aetiology and the role of the thymus in EAMG are still unclear, this parallelism suggests that the primary sensitization of autoreactive lymphocytes may occur in the thymus by contact with thymically expressed AChR-like proteins; these, in turn, may share epitopes with the neuromuscular AChR and give rise to pathogenetically relevant cross-reactivity [review: 102].

Anti-AChR antibodies play a pivotal role in the pathogenesis of EAMG, since the disease can be adoptively transferred in mice with immunoglobulins from myasthenia gravis (MG) patients [103]. Active immunization of rodents with purified AChR can reproduce the clinical and histopathological features of MG [104]; the resulting antibody response is directed to a small extracellular region of the a subunit of the AChR, called the main immunogenic region (MIR) [review: 104]. MIR-specific antibodies are highly cross-reactive, and a single monoclonal MIR antibody can inhibit up to 60% of the binding of anti-AChR antibodies from MG patients [105]. In addition, MIR-specific antibodies can adoptively transfer disease in naive animals [105]. Epitope-mapping studies have localized the MIR to a region around amino acid residues 67–76 of the a subunit of the AChR [106, 107]. The autoantibodies cause loss of functional AChR by a combination of complement-medicated lysis [103] and an increased rate of AChR internalization by the muscle cell [108]. Since high affinity complement-fixing antibodies are crucial to the pathogenesis of EAMG, the intervention of AChR-specific $CD4^+$ T cells must be postulated [107]. In contrast to the restricted type of antigen recognition by B cells, the $CD4^+$ T cells seem to respond to a variety of distinct epitopes on the AChR [review: 107]; this feature questions the feasibility of therapeutic approaches aimed at tolerizing antigen-specific T cells in this disorder.

Discussion

The review on pathogenetic aspects of the various autoimmune models clearly indicates the diversity of mechanisms relevant in different pathologies. This variability is most striking in the organ- and tissue-specific autoimmune diseases, in which special anatomical conditions contribute to maintain a status of tolerance. The blood-brain barrier in the CNS, for example, keeps the autoantigens relatively hidden from immunocompetent cells, whereas in the eye the lack of lymphatic drainage, in concert with active suppression mechanisms, creates an immunoprivileged microenvironment around the autoantigens. These conditions are quite different from those present in joint cartilage, where antigens are physiologically more exposed to the immune system, and naturally occurring autoreactive lymphocytes may have been partially tolerized to their respective antigens. The contribution of lymphocyte subsets to tissue pathology varies considerably among models: in NOD mice with IDDM there is a clear involvement of both $CD8^+$ and $CD4^+$ T-cell subsets; in EAE, $CD8^+$ T cells are relevant, but Th1-polarized $CD4^+$ T cells appear to predominate; in CIA, in turn, the most obvious feature seems the cognate interaction between $CD4^+$ T cells and B cells; finally, in EAMG humoral rather than cellular responses seem to dictate the development of the disease. For these reasons, particular features that may offer selective or specific options for immunotherapeutic intervention are most likely to differ among the disease models.

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