Multiple sclerosis: MHC associations and therapeutic implications

Samantha Holmes, Manuel A. Friese, Christian Siebold, E. Yvonne Jones, John Bell and Lars Fugger

Multiple sclerosis (MS) is an autoimmune disease with an important genetic component. The strongest genetic association is with the major histocompatibility complex (MHC) region. Several MHC alleles predispose to the disease, the most prominent of which are certain alleles in the HLA-DR2 haplotype. Functional and structural studies have helped to explain the molecular basis of these associations. Although there is currently no curative treatment for MS, an increased understanding of the disease has aided the design of immunotherapies that act on the immune system more specifically than the longstanding drugs. Many of these therapies work at the antigen-specific level, disrupting the interaction between T-cell receptors and MHC molecules that leads to disease.

The pathogenic concepts surrounding multiple sclerosis (MS) are continually changing. Progress in biotechnology, together with developments in magnetic resonance imaging (MRI) and in the design of clinical studies, has led to an array of experimental and therapeutic possibilities.

Samantha Holmes, PhD student, E-mail: samantha.holmes@ccc.ox.ac.uk
Christian Siebold, Postdoctoral fellow, E-mail: christian@strubi.ox.ac.uk
E. Yvonne Jones, Professor of Structural Biology, E-mail: yvonne@strubi.ox.ac.uk
Division of Structural Biology, The Henry Wellcome Building for Genomic Medicine, The University of Oxford, Roosevelt Drive, Oxford, OX3 7BN, UK. Tel: +44 (0)1865 287708; Fax: +44 (0)1865 287547

Manuel A. Friese, Postdoctoral fellow, E-mail: manuel.friese@imm.ox.ac.uk
Lars Fugger (corresponding author), Professor of Clincal Immunology, E-mail: lars.fugger@imm.ox.ac.uk
MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, The University of Oxford, Oxford, OX3 9DS, UK. Tel: +44 (0)1865 222351; Fax: +44 (0)1865 222502

John Bell, Regius Professor of Medicine, Nuffield Dept of Clinical Medicine, John Radcliffe Hospital, The University of Oxford, Oxford, OX3 9DU, UK. Tel: +44 (0)1865 221339; Fax: +44 (0)1865 220993; E-mail: regius@medical-sciences-office.oxford.ac.uk

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However, the disease is still not curable and the development of new drugs with fewer side effects and greater specificity than existing treatments is vital. Understanding the aetiology and pathogenesis of MS is crucial to achieving this goal.

Immunopathogenesis of MS

MS is a chronic demyelinating disease of the central nervous system (CNS) (reviewed in Ref. 1). Recurrent inflammatory attacks against the white matter of the brain lead to the formation of plaques and ultimately to neurodegeneration. Common clinical manifestations include visual impairment, disruption of motor functions such as walking and fine finger movements, bowel and bladder incontinence, incoordination, and sensory disturbances. MS usually first presents in young adulthood and has a variable disease course: relapsing-remitting, primary progressive (the gradual progression of disease from its onset) and secondary progressive (an initial relapsing-remitting course followed by the steady progression of disease). The disease affects approximately one million people worldwide, with two times as many women being affected as men (Ref. 2).

The aetiology of MS is unknown, but an autoimmune pathogenesis is suggested by an association with genes in the major histocompatibility complex (MHC) region on chromosome 6, as well as the presence of inflammatory infiltrates of T and B cells in the brain and spinal cord of affected individuals (Refs 3, 4, 5). A pathogenic scenario has been proposed based on studies in MS patients (Ref. 6) and animal disease models (Ref. 7) (Fig. 1). According to this model, $CD4^+$ T cells that are autoreactive against myelin proteins escape tolerance induction (the process by which specific unresponsiveness to host antigens is normally achieved), and become activated in the peripheral immune system. Upon activation, these cells are able to breach the blood–brain barrier (BBB) and migrate into the CNS. In the CNS, the $CD4^+$ T cells find their target structures and become reactivated. The reactivated cells, accompanied by $CD8^+$ T cells, macrophages and microglial cells, secrete cytokines, typically of T helper 1 (Th1) type, including tumour necrosis factor (TNF)-α and interferon (IFN)-γ. B cells and autoantibody-activated complement proteins also pass through the leaky BBB. Together, these components mediate local tissue damage. Eventually, the demyelination of nerve fibres impairs electrical conduction along neuronal axons and this, together with the widespread development of a dense fibrous network of neuroglia (gliosis), leads to the clinical manifestations described above (Refs 2, 7, 8).

Genetics of MHC associations in MS

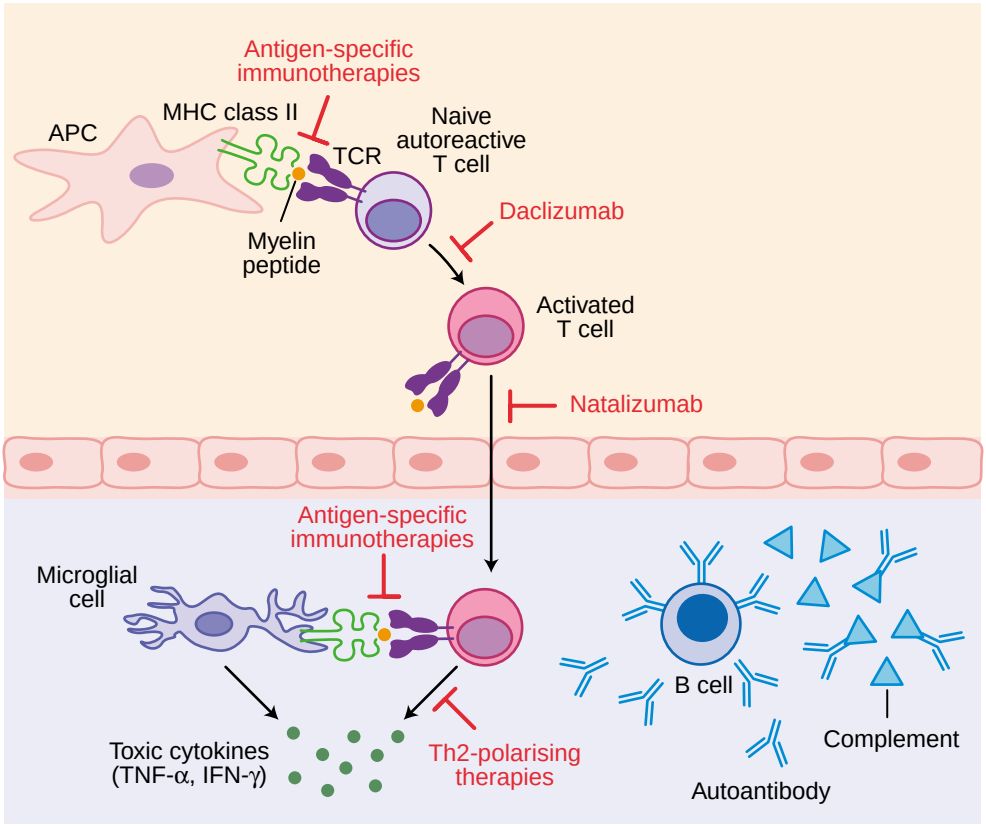
Several autoimmune diseases are associated with certain MHC class II alleles. Insulin-dependent diabetes mellitus is associated with alleles belonging to the HLA-DR3 and HLA-DR4 haplotypes (Ref. 9), rheumatoid arthritis with HLA-DR4 alleles (Ref. 10) and coeliac disease with HLA-DQ2 and HLA-DQ8 alleles (Refs 11, 12), to give but a few examples. Familial aggregation of MS indicates that this disease also has a significant genetic component (Ref. 13). The observed patterns of inheritance suggest that MS is a complex trait that is governed by multiple loci, each exerting a small effect on overall risk, rather than by a single disease gene. Genes in the MHC region have consistently been shown to exert the strongest influence on disease susceptibility. In particular, the disease has been associated with the HLA-DR2 haplotype, which contains three β-chain-encoding alleles: DRB1*1501, DRB5*0101 and DQB1*0602. The former two alleles encode β chains of different HLA-DR2 molecules and the latter allele encodes a β chain of an HLA-DQ6 molecule. HLA-DR2 carries a fourfold relative risk for northern European Caucasoids (Refs 14, 15, 16) and about two thirds of MS patients are $HLA\text{-}DR2^+$ (Ref. 7).

A recent study has shown that there is a dose effect of HLA-DR2 on disease risk and severity. Two copies of the susceptibility haplotype (i.e. *DR2*/*DR2*) lead to increased disease risk relative to individuals of the *DR2*/*DRX* genotype (where X denotes other DR alleles). Moreover, there is an increase in severe MS and a concurrent decrease in benign MS in DR2-homozygous individuals in comparison with DR2 heterozygotes, indicating that HLA-DR2 has disease-modifying effects (Ref. 17). Another study has shown that $HLA\text{-}DR2^+$ MS patients have a slightly younger average onset age compared with $HLA\text{-}DR2^-$ patients (Refs 18, 19).

Extensive linkage disequilibrium (LD; the inheritance of some genes together more than expected) within the MHC region, makes it difficult to establish which allele within a given

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The pathogenesis of multiple sclerosis (MS) and points of therapeutic intervention

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Figure 1. The pathogenesis of multiple sclerosis (MS) and points of therapeutic intervention. Myelin-reactive T cells in the peripheral blood are activated through binding of their TCR to myelin peptide presented by MHC on an APC, and are able to penetrate the BBB. In the CNS, the cells are reactivated by their target antigens. Toxic cytokines such as TNF-α and IFN-γ, secreted by T cells and APCs, alongside antibodies and complement proteins, mediate disease-associated tissue damage. Points of therapeutic intervention in this process are indicated by red blocking arrows. Abbreviations: APC, antigen-presenting cell; BBB, blood–brain barrier; CNS, central nervous system; IFN, interferon; MHC, major histocompatibility complex; MS, multiple sclerosis; TCR, T-cell receptor; Th2, T helper 2; TNF, tumour necrosis factor.

haplotype is associated with a phenotype. This has been a problem in the case of the MS-associated DRB1*1501, DRB5*0101 and DQB1*0602 alleles, which are in strong LD in most populations. In African Americans, the DRB1*1501 and DRB5*0101 alleles do not display the high degree of LD with the DQB1*0602 allele that is characteristic of Europeans. A study carried out in a large African American cohort showed DRB1*15 chromosomes carrying non-*0602 DQB1 alleles to be significantly increased in MS patients, whereas chromosomes carrying the DQB1*0602 allele with other DRB1 alleles (i.e. not DRB1*15 alleles) were present at identical frequencies in patients and controls. This selective association of disease with DRB1*15 indicates that DRB1*1501, rather than DQB1*0602, constitutes the principal MS disease-risk gene (Ref. 20). However, a modulating role of the HLA-DQ6 allele on clinical outcome cannot be discounted, and three studies have shown that the DQB1*0602 allele might confer relatively weak HLA-DR-independent disease susceptibility in other populations (Refs 21, 22, 23).

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Although the HLA-DR2 haplotype is most commonly associated with MS, there is some variation in the known HLA class II associations between different populations (Table 1). Studies carried out in the Sardinian population, for example, showed MS to be associated with the HLA-DR3 (DRB1*0301–DQA1*0501–DQB1*0201) and HLA-DR4 (DRB1*0405–DQA1*0501–DQB1*0301) haplotypes (Ref. 24) in addition to HLA-DR2 (Ref. 25). There is also evidence to suggest that loci other than DRB1 and DQB1 within the MHC region contribute to disease susceptibility. A study of MHC association in the Sardinian MS population revealed additional associations with the HLA class II DPB1 locus and a microsatellite in the HLA class I area (Ref. 25). Other studies have also documented associations with class I microsatellites (Refs 26, 27), and two studies have shown the HLA-A*0301 allele to increase the risk of MS independently of DRB1*1501 and DQB1*0602 (Refs 28, 29).

Molecular basis of MHC associations in MS and related functional studies

The T-cell repertoire in MS

The mechanism by which MHC genes predispose individuals to a particular autoimmune disease is unknown. A popular hypothesis is that disease-associated MHC class II molecules trigger disease through the presentation of foreign or autoantigenic peptides, which are recognised by T-cell receptors (TCRs) on autoreactive $CD4^+$ T cells (Ref. 30). Consequent activation of these T cells enables them to mediate the inflammation and tissue destruction that is characteristic of the autoimmune disease. Consistent with this scenario, potentially autoreactive T cells have been found in the T-cell repertoire of normal individuals, but they usually persist in a quiescent state (Ref. 31). A certain MHC allele might predispose to a particular disease because of a bias in the repertoire of peptides that it binds. The allele might preferentially bind peptides that cause autoreactive T cells to become activated in the peripheral lymphoid tissues, resulting in tissue destruction and disease. As well as presenting antigen to $CD4^+$ T cells in the periphery, MHC class II molecules have an important role in mediating negative and positive selection of the T-cell repertoire, which takes place in the thymus. In the thymus, disease-associated alleles may bind peptides in such a way that autoreactive T cells escape tolerance induction. For example, a low-affinity interaction between an MHC class II molecule and an autoantigenic peptide may result in the complex being present in the thymus at a concentration that is too low to mediate the negative selection of responding T cells. Another possibility is that the disease-associated alleles are unable to mediate the positive selection of regulatory T cells, which are important in the inhibition of autoreactivity. These various explanations for the association of autoimmune diseases with MHC class II alleles are not

Table 1. Major histocompatibility complex (MHC) associations in multiple sclerosis (MS)

MHC class	Genetic associations	Odds ratio (increased risk of disease)	Refs
I	HLA-A*0301	1.9–2.1 (northern European Caucasoid populations)	28, 29
II	HLA-DR2 haplotype (DRB1*1501–DRB5*0101–DQB1*0201)	2.9–3.6 (northern European Caucasoid populations)	28, 29
	HLA-DR3 haplotype (DRB1*0301–DQA1*0501–DQB1*0201)	1.7 (Mediterranean populations)	25
	HLA-DR4 haplotype (DRB1*0405–DQA1*0501–DQB1*0301)	2.2 (Mediterranean populations)	25
	Alleles of the HLA-DPB1 locus (e.g. DPB1*0301)	1.6 (Mediterranean populations)	25

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mutually exclusive and probably all contribute, to varying degrees.

Autoantigens in MS

The target autoantigens in MS, which are presented by MHC class II molecules to TCRs, are still not known with certainty. However, diseases resembling MS both clinically and pathologically, collectively referred to as experimental autoimmune encephalomyelitis (EAE), can be induced in susceptible strains of mice through immunisation with CNS-derived proteins. Candidate autoantigens include three components of the myelin sheath – myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) (Ref. 32) – and the presence of T cells that are reactive towards these antigens has been observed in MS patients (Refs 33, 34, 35, 36).

One immunodominant MBP T-cell epitope has been identified as MBP residues 85–99 in MS patients who are HLA-DR2$^+$ (Ref. 37). The MBP(85–99) peptide binds with high affinity to the DR2 molecule containing the DRB1*1501 β chain. Structural analysis of different DRβ chains gives an insight into variation in peptide-binding properties that might provide a possible mechanism to explain the association of particular alleles with disease susceptibility. As an example, the crystal structure of DRB1*1501 (Ref. 38) differs from other, non-DR2-related, DRβ chains owing to the presence of a large hydrophobic pocket (denoted P4) in the peptide-binding groove. This pocket displays high affinity for aromatic amino acids and accommodates the primary anchor residue for peptide binding to this DR2 molecule. When complexed with the MBP immunodominant epitope, the P4 pocket is occupied by phenylalanine, located at residue 92 of MBP. The polymorphic residue at DRβ position 71 contributes to the P4 pocket, and an alanine residue at this position, which is observed only in DR15 alleles and one DR13 allele, is crucial in providing the space that is necessary for the phenylalanine aromatic side chain (Ref. 38).

Humanised mouse models of MS

The role of HLA-DR2 alleles in MS has been further defined through the development of humanised mice. Such mice can be engineered to express various combinations of human proteins that are relevant to MS. HLA-DR2-transgenic mice have been generated that express the DRB1*1501 allele, as well as the human CD4 co-receptor and a TCR from the MS-patient-derived T-cell clone Ob.1A12, which is specific for the DRB1*1501–MBP(85–99) complex. On immunisation with MBP, these mice develop CNS inflammation and demyelination, leading to clinical manifestations that resemble those seen in MS. Interestingly, although 4% of these mice develop spontaneous disease, this percentage is increased when the TCR and DR2 molecule are expressed on a *RAG2*$^{-/-}$ background (Ref. 39). Since the *RAG2* gene is required for endogenous TCR rearrangements, its mutation might lead to an absence of regulatory T cells that would normally protect against disease.

HLA-DR2-transgenic mice have also been used to induce and isolate an antibody specific for the MBP(85–99) peptide presented in the context of DR2 (DRB1*1501). The mice were immunised with the DRB1*1501–MBP(85–99) complex and mice producing antibodies of appropriate specificity were used to generate phage display libraries of antibody Fab fragments from which the clone was selected. Immunohistochemical studies with this antibody, carried out using brain samples from MS patients, have shown that the DRB1*1501–MBP complex is presented by antigen-presenting cells (APCs), primarily microglial cells, in MS lesions. The antibody also stained APCs in normal brain tissue from HLA-DR2$^+$ individuals, but with a lower frequency and staining level when compared with staining in MS patients. Moreover, the presence of T cells adjacent to these APCs was only observed in MS patients and not in the HLA-DR2$^+$ controls (Ref. 40).

The concordance rate of MS in monozygotic twins is only 30%, indicating that environmental factors play an important role in the disease, besides the genetic contributions (Ref. 41). Viral infections are often associated with relapses in MS and thus it has been suggested that they may be involved in disease initiation and perpetuation. Several mechanisms have been proposed to explain how infection could lead to a breakdown in self-tolerance, resulting in autoimmune disease. One such theory, termed molecular mimicry, hypothesises that T cells generated in response to an infectious agent crossreact with a self-antigen, which shares sequence or structural homology with a viral peptide (Fig. 2). A number of other antigen-nonspecific theories exist that are collectively referred to as bystander activation (i.e.

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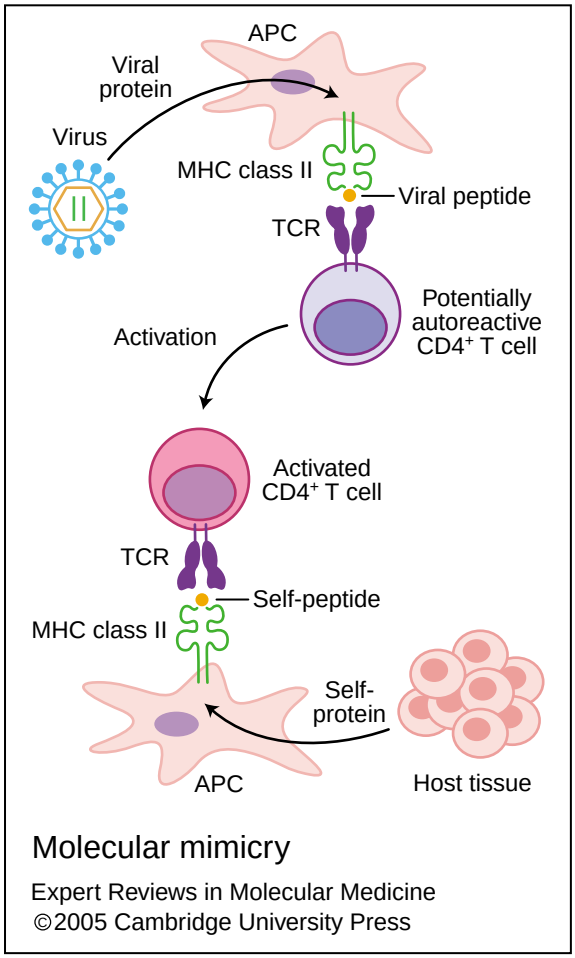


Figure 2. Molecular mimicry. A potentially autoreactive T cell, possessing TCRs that recognise both a foreign (viral) peptide and a self-peptide, is activated by a virus-derived peptide. Thus, in addition to mediating an antiviral response, the T cell is also capable of mediating self-directed responses. This phenomenon has been termed molecular mimicry. Abbreviations: APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

the activation of T cells that are specific for a particular antigen during an immune response against an unrelated antigen; such activation is thought to occur as a result of the general proinflammatory environment induced by infection).

The first structurally validated example of molecular mimicry has recently been provided through X-ray crystallography (Ref. 42). Although the DRB1*1501 allele has received the most attention, there are two DR alleles in the HLA-DR2 haplotype, and the association of disease with DRB5*0101 is as strong as with the DRB1 locus (Ref. 43). A TCR from the MS-patient-derived T-cell clone Hy.2E11 is crossreactive with the two different DR2 molecules, recognising MBP(85–99) in the context of DRB1*1501 and a peptide from Epstein–Barr virus, EBV(627–641), in the context of DRB5*0101 (Ref. 42). Double-transgenic mice were generated expressing the Hy.2E11 TCR along with either the DRB1 or DRB5 molecule, and a triple-transgenic mouse was also generated expressing the TCR alongside both DRB1 and DRB5. When spleen cells from the mice were cultured in vitro with the EBV and MBP peptides, T cells from the DRB1 mouse responded only to the MBP peptide, whereas those from the DRB5 mouse responded only to the EBV peptide. T cells from the triple-transgenic mouse responded to both peptides. X-ray crystallographic studies established the structural basis for this crossreactivity, demonstrating pronounced structural equivalence between the DRB1–MBP and DRB5–EBV complexes at the surfaces presented to the TCR (Ref. 42). Although there is no conclusive evidence for an association between MS and EBV, the fact that DRB1*1501 and DRB5*0101 are inherited together suggest that the EBV and MBP peptides could be sequentially presented to the same TCR, leading to the activation of a pathogenic T-cell line. If this is the case, a haplotype such as HLA-DR2, which encodes two MHC molecules between which molecular mimicry can occur, would be particularly likely to be associated with autoimmune disease.

The Ob.1A12 TCR also displays crossreactivity between two MHC class II molecules, in this case DR2 (DRB1*1501) and DR4 (DRB1*0401) (Ref. 44). The MS patient from whom the Ob.1A12 clone was derived was heterozygous for these two alleles and both loci are linked with genetic susceptibility to MS (Refs 45, 46). An altered peptide ligand (APL) derived from MBP(85–99) with a single amino acid substitution (Val88 to Lys) stimulated the TCR in the context of both molecules, although in the absence of this mutation the MBP(85–99) peptide is not recognised by this TCR when presented in the context of the DR4 molecule. The Ob.1A12 TCR was already known to be highly crossreactive as five microbial peptides have previously been shown to activate this T-cell clone when presented in the context of DR2 (DRB1*1501) (Ref. 47). A high degree of degeneracy might well be a general

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feature of autoreactive TCRs as it would greatly facilitate the crossreactivity associated with molecular mimicry.

Several immunodominant T-cell epitopes other than MBP(85–99) have been identified in MS patients and used in corresponding functional studies. These include PLP(95–116) (Ref. 48) and MBP(111–129) (Ref. 46). Like MBP(85–99), PLP(95–116) is presented in the context of DR2 (DRB1*1501). This epitope also appears to be presented by the DR2 (DRB1*1502) molecule (Refs 48, 49), which might predispose to MS in the Japanese population (Ref. 50). Adoptive transfer experiments have been carried out in which a PLP(95–116)-specific T-cell line, generated in DR2 (DRB1*1502)-transgenic mice, was introduced into DR2 (DRB1*1502)-transgenic mice on the *RAG2*$^{-/-}$ background. Four out of seven of these mice developed EAE manifestations (Ref. 50). The MBP(111–129) epitope is immunodominant in the context of DR4 (DRB1*0401) (Ref. 46). HLA-DR4 genes have been found to be associated with MS particularly in patients of Mediterranean origin (Refs 51, 52, 53). MBP(111–129) is a less common encephalitogen than MBP(85–99). However, the MBP(111–129)-specific T-cell clone MS2-3C8, isolated from an MS patient, has recently been shown to induce EAE when adoptively transferred into DR4 (DRB1*0401)-transgenic mice (Ref. 54).

Interestingly, EAE induced by PLP(95–116)- and MBP(111–129)-specific T cells exhibited different phenotypes with unique features. The DR2 (DRB1*1502)-transgenic mice into which PLP-reactive T cells were transferred displayed ataxia without paralysis, whereas classical EAE is characterised by ascending paralysis (Ref. 50). By contrast, the DR4 (DRB1*0401)-transgenic mice into which MBP-reactive T cells were transferred displayed ascending paralysis but, in addition, this EAE was characterised by dysphagia (difficulty in swallowing) as a result of restricted jaw and tongue movements (Ref. 54). Around 30–40% of MS patients develop dysphagia in the later stages of the disease course (Refs 55, 56, 57). Similar distinct disease features have been observed in mice that are transgenic for a MOG-specific TCR. These mice developed spontaneous optic neuritis with no other EAE symptoms (Ref. 58). Optic neuritis is a common initial feature of MS in 30–60% of patients (Ref. 59). Such observations have led to a growing opinion that there is a correlation between disease phenotype and both the MHC class II background and the recognised antigen. This could account in part for the heterogeneous nature of MS in terms of symptoms and disease courses.

Mouse models have clearly been of great value in studying numerous diseases, but it should be noted that there are also some shortcomings when they are employed to study a human disease. This issue has recently been addressed more extensively in Ref. 60 and will not be discussed further here.

Clinical implications

An increased understanding of the molecular mechanisms that underlie MS has been important in the development of innovative therapies. There is currently no effective treatment for the disease, although a variety of drugs are used, which have some effect in a proportion of patients. Unfortunately, the broadly immunosuppressive corticosteroids that have been used for more than 40 years to treat MS patients have a variety of unwanted side effects. As a result, other therapies are being sought (Table 2).

Immunomodulatory drug therapies

Recently, several immunomodulatory treatments have been developed that act on the immune system more specifically than coticosteroids. The most widely used immunomodulatory drugs are IFN-β and glatirimer acetate (GA). IFN-β and GA were initially found to be successful in the treatment of EAE as early as the 1980s and 1970s, respectively (Refs 61, 62, 63, 64, 65, 66), before being taken into trials in relapsing-remitting MS patients (Refs 67, 68, 69, 70, 71, 72, 73), where they have been found to reduce the relapse rate of MS by 30% (Refs 74, 75).

The mechanism by which the antiviral cytokine IFN-β modifies MS is uncertain but suggestions include a reduction in MHC class II expression in the brain (Ref. 76) or in the metalloproteinase activity that is important for lymphocyte migration to the CNS (Ref. 77). Alternatively, the antiviral properties of the cytokine may be directly responsible for its effects.

GA, also known as Cop 1 and poly(Y, E, A, K)n, is a random synthetic amino acid copolymer composed of the residues Y, E, A and K (Ref. 63). Its design was based on the binding motif of the immunodominant MBP(85–99) epitope to HLA-DR2. It was originally thought that GA acts by blocking the peptide-binding cleft of the

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Table 2. Important ongoing studies in the treatment of multiple sclerosis (MS) (Ref. 126)

Therapy	Characteristics	Company	Study design
TM-27 (ATM027)	Human monoclonal anti-Vβ5.2/5.3 antibody	Avant Immunotherapies	Double-blind, placebo-controlled, Phase II completed
CDR2 BV6S26S5 (IR-208)	Synthetic peptide, vaccine of TCR Vβ6 in incomplete Freund's adjuvant	The Immune Response	Phase I open trial
TCR peptide (NeuroVax™)	Vβ5.265131.1, in combination with three different TCR peptides	The Immune Response	Phase I, comparing intramuscular application versus intradermal versus placebo
T-cell vaccination	Reduction of myelin-specific immune response	Academia	Different trials (open and double-blind)
Daclizumab (Zenapax®)	Anti-IL-2Rα (CD25)	Roche Pharmaceuticals	Open study, NIH (Bethesda, USA)
Campath-1 (Alemtuzumab®)	Chimaeric anti-CD52 antibody	Millennium, BTG International, ILEX Oncology, Burroughs, Schering AG	Trial comparing with IFN-β1a
Rituximab (Rituxan®, Mabthera, IDEC-C2B)	Chimaeric anti-CD20 antibody	Genentech	Open trial at Washington University (St Louis, USA)
Natalizumab (Tysabri®)	Human monoclonal anti-α4β1 integrin	Biogen Idec, Elan Corporation	Two multi-centre Phase III studies (AFFIRM, SENTINEL) and a study with Copaxone® (Colance)

Abbreviations: IFN, interferon; IL-2R, interleukin 2 receptor; TCR, T-cell receptor.

disease-associated HLA-DR2 molecule, thus inhibiting the binding of the autoantigenic peptide to the MHC molecule and the subsequent activation of the autoreactive TCR. However, in recent years, other mechanisms of action have been proposed for GA, including immune deviation [polarisation of cytokine production by T cells to the T helper 2 (Th2) type] and induction of regulatory T cells.

Antigen-specific immunomodulatory therapies

Several antigen-specific immunomodulating therapies have now been designed that either interfere with antigen presentation to autoreactive T cells by human MHC class II molecules or induce tolerance to the antigen. A potential problem with such treatments is the phenomenon known as epitope spreading. Although T cells responding to one particular epitope from an autoantigen might initiate a disease such as MS, as the response persists it tends to broaden. Thus, T cells with additional specificities are recruited and inflammatory responses to several epitopes, which might originate from the same or different proteins (intra- or inter-molecular spreading), can develop (Ref. 78). Drugs that target one particular antigen would obviously be rendered far less effective given such a scenario. One method of combating this problem uses DNA plasmids encoding several myelin proteins. These plasmids have been designed based on microarray analysis of autoantigens targeted in mice with EAE. The DNA vaccine reduces the relapse rate by 50% in these mice and appears to suppress responses against multiple antigens: MBP, MOG and PLP (Ref. 79). A Phase I trial with such DNA vaccines has now been approved.

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GA also overcomes the problem of epitope spreading, by binding promiscuously to MHC class II molecules. The copolymer has been found to bind to HLA-DR1 and HLA-DR4 molecules (Ref. 80) and a mouse HLA-DQ homologue (I-A^s; Ref. 81), in addition to HLA-DR2 molecules. This enables it to compete with a variety of peptides in binding to their respective MHC class II partners and thus simultaneously tolerises against different antigens. For example, the murine I-A^s molecule is the only MHC class II molecule expressed in the EAE-susceptible SJL/J mouse strain. Significantly, although the design of GA is based on an MBP epitope, the drug suppresses disease induced by the encephalitogenic PLP(139–151) peptide in this murine model (Ref. 82). Several novel, random, synthetic amino acid copolymers have now been generated in the same way as GA, in an effort to develop copolymers that bind more tightly to HLA-DR2 and thus are more effective than GA in the treatment of MS. In one study, two copolymers, poly(Y, F, A, K)n and poly(F, A, K)n, were shown to be more efficient than Cop 1 both in inhibiting DR2-MBP(85–99)-specific T-cell clones and in suppressing PLP(139–151)-induced EAE in the SJL/J mouse (Ref. 83). In recent follow-up studies, two copolymers, poly(F, Y, A, K)n and poly(V, W, A, K)n, were developed that are more effective than GA at suppressing EAE, not only in the PLP-induced SJL/J model (Ref. 81) but also both in an MBP-induced humanised mouse model made transgenic for HLA-DR2 and an HLA-DR2–MBP(85–99)-specific T-cell clone derived from an MS patient (Ref. 84). Both models were used to study the mechanisms by which the copolymers exert their effects. Interestingly, it seems that the two copolymers might operate differently from one another, with poly(F, Y, A, K)n using induction of regulatory T cells and immune deviation as its principle mechanisms, and poly(V, W, A, K)n acting primarily as a blocking agent or TCR antagonist. In both models, poly(F, Y, A, K)n was found to induce proliferation of copolymer-specific T-cell lines and production of suppressive Th2-type cytokines by both the copolymer-specific T cells and, to some extent, antigen-specific T cells. By contrast, although only in the humanised mouse model, poly(V, W, A, K)n induced anergy of HLA-DR2-restricted transgenic T cells. Overall, poly(V, W, A, K)n was slightly more effective at suppressing EAE. The authors suggest that a combination of mechanisms might explain copolymer action and thus a combination of copolymers could be the most effective treatment for disease.

Further approaches to antigen-specific immunotherapy include oral tolerisation, APLs and recombinant T-cell ligands (RTLs). In mouse models, oral administration of low doses of myelin antigens desensitises the immune response that is responsible for EAE, possibly by the induction of regulatory T cells (Ref. 85). However, attempts to induce oral tolerance in humans have thus far been unsuccessful (Ref. 86). APLs are peptide analogues in which one or more of the amino acids in the native peptide has been substituted, usually at TCR contact positions. They act as partial agonists or antagonists, altering T-cell responses through immune deviation or induction of regulatory T cells. APLs for MBP (in the region of the pathogenic 85–99 epitope) have successfully reversed EAE in rodent models (Refs 87, 88). Unfortunately, the treatment of MS patients with APLs to date has been less successful than was expected on the basis of the mouse experiments (Refs 89, 90). One side effect in a proportion of patients is an increase in allergic responses (this is also observed in patients taking GA), which is associated with the Th2 polarisation induced by the APL (Ref. 90). The finding that the Ob.1A12 TCR is capable of reacting with an APL presented in the context of two MHC molecules (see previous section) might also provide an explanation. The authors suggest that the injection of APL into patients heterozygous for MHC class II molecules could result in unexpected crossreactivities leading to activation of autoreactive T cells (Ref. 44). RTLs have also had tolerance-inducing effects in mouse models. An RTL consists of the extracellular domains of a class II molecule associated either covalently or noncovalently with a pathogenic peptide. The MOG(35–55) peptide, which has been shown to induce EAE in HLA-$DR2^+$ mice, has been covalently linked to the α_1 and β_1 domains of the DR2 (DRB1*1501) molecule to produce one such RTL. Treatment of the transgenic mice with the ligand was found to induce nonresponsiveness to the MOG(35–55) peptide in T cells. The secretion of Th1 cytokines was reduced and ultimately the clinical and histological signs of EAE were reversed (Ref. 91). Similar RTL constructs have been found to suppress MBP-induced EAE in Lewis rats (Refs 92, 93).

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One final approach to antigen-specific immunotherapy is through the use of antigen-specific humanised monoclonal antibodies (mAbs). A mAb specific for an I-A^s–MBP complex was found to inhibit EAE in H-2^s mice (Ref. 94) and it is hoped that the MK16 mAb (mentioned previously in this review), which recognises MBP(85–99) in the context of HLA-DR2, may have some clinical relevance in the treatment of human MS in the future.

Antibody and T-cell-mediated therapy

Antibodies or T cells that are reactive with candidate autoantigens and disease-associated MHC class II molecules could themselves be used as tools to deliver therapeutic compounds, such as suppressive cytokines, to dendritic cells at the site of inflammation. Such an approach has already been employed with some success in one laboratory: MBP-reactive T-cell hybridomas, retrovirally transduced to express interleukin (IL)-4, were capable of trafficking to autoimmune lesions in the CNS to ameliorate EAE (Ref. 95) and, in a subsequent experiment, the same method was used to deliver the p40 subunit of IL-12, a Th1 cytokine antagonist, again reducing clinical disease (Ref. 96). This localised delivery of suppressive cytokines is one way of avoiding the nonspecific toxicity associated with their systemic delivery.

Another therapeutic strategy is to deplete MBP-specific T cells in MS patients. A specific expansion of T cells expressing the variable chain Vβ5.2/5.3$^+$ has been demonstrated in peripheral blood (Refs 97, 98), cerebrospinal fluid (CSF) (Ref. 99) and brain lesions (Ref. 15) of MS patients. This expansion has been most consistently observed in HLA-DR2$^+$ patients (Ref. 98). Vβ5.2/5.3$^+$ T cells can be activated by MBP, and depletion of these T cells in vitro decreases MBP reactivity. On the basis of these observations, a humanised mAb, ATM-027, was developed that specifically targeted Vβ5.2/5.3$^+$ T cells. Two small studies were carried out investigating the feasibility of this approach. The first study showed no toxic effects from the antibody and, in serial MRI investigations, a reduction in disease lesions was observed in the treated group, although this trend did not reach statistical significance (Ref. 100). The second study showed the selective depletion of Vβ5.2/5.3$^+$-expressing T cells to be effective over an 18-month period, resulting in a decrease in potentially disease-promoting anti-MBP reactivity and pro-inflammatory cytokine production (Ref. 101).

Depletion of myelin-reactive T cells has also been achieved by T-cell vaccination (TCV). This approach involves immunisation of MS patients with irradiated MBP-reactive T-cell clones. In a pilot trial, held for two years, disease exacerbations decreased in several vaccinated MS patients and the increase in brain lesion size slowed down in treated individuals, compared with controls (Ref. 102). Two recent studies used TCV with activated, irradiated CD4$^+$ T cells, derived from the CSF or peripheral blood, respectively. Almost all treated patients showed a stabilisation of neurological disability during either the two-month treatment period (Ref. 103) or the one-year follow-up period (Ref. 104). These promising results will lead to a bigger, double-blind, placebo-controlled trial.

The approaches described so far all target the myelin-specific T cells, either at the MHC class II molecule or at the TCR. However, there are several other significant pathogenetic pathways that are subsequent to T-cell activation (Fig. 1). The receptors CD25 and CD52 are important for complete activation of pathogenic T cells, and activated T cells require certain surface molecules to infiltrate the CNS. Humanised mAbs are convenient tools to block these receptors specifically and they have been used with varying degrees of success in the treatment of MS. Daclizumab is one such antibody, recognising CD25, the IL-2 receptor α chain, which is expressed on activated T cells. Blockade of the IL-2 signalling pathway limits T-cell expansion, providing a less-aggressive form of immunosuppression than, for example, steroids. In a Phase II trial, daclizumab led to a 78% reduction in new lesions in MS patients failing to respond to IFN-β. A recent clinical trial has shown that monotherapy with daclizumab is safe and has potential for therapeutic benefit in relapsing-remitting and secondary progressive MS patients (Ref. 105). The antibody is used in the treatment of solid-organ graft rejection and immune-mediated uveitis, where long-term administration has not led to an increase in infections (Ref. 106). Alemtuzumab® is a lymphocyte-depleting antibody that binds to the CD52 molecule, which is expressed on a variety of cells including T cells, B cells, monocytes and thymocytes. Treatment of MS patients with the antibody reduced the number of relapses and inflammatory lesions

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(Refs 107, 108). However, around a third of these patients developed autoimmune hyperthyroidism (Grave's disease; Ref. 109). Natalizumab is an antibody against the α4 chain of the α4β1 integrin. This integrin, expressed on the surface of activated T cells and monocytes, is a key homing molecule, mediating migration of these cells into the CNS. The antibody acts as an antagonist to the integrin, blocking its binding to vascular cell adhesion molecule 1 (VCAM-1), which is necessary for the inflammatory cells to cross the BBB. The antibody recently decreased the frequency of relapses by 50% in a Phase II clinical trial, as well as reducing the formation of disease lesions by 90% (as assessed by MRI) in comparison with the 50–80% reduction observed with IFN-β and the 30% reduction observed with GA (Ref. 110). Similarly, administration of α4 integrin has been shown to ameliorate EAE by preventing pathogenic T cells from entering the CNS (Ref. 111).

Other therapies

Finally, there are some existing medications that are used to treat other, non-autoimmune diseases that have also shown potential in the treatment of MS. These include: mitoxantrone, primarily used to treat malignant disorders (Ref. 112); antihistamines, commonly used to treat allergy (Ref. 113); and angiotensin blockers (Ref. 114), statins (Ref. 115) and peroxisome proliferation activated receptor (PPAR-α) antagonists (Ref. 116), used to treat various aspects of atherosclerosis such as hypertension, hypercholesterolaemia and hypertriglyceridaemia, respectively. These drugs have a generally broad and nonspecific mode of action.

In a Phase II clinical trial, patients receiving intravenous mitoxantrone, administered in combination with a steroid treatment, showed a significantly reduced number of disease lesions and relapses compared with patients receiving the steroid only (Ref. 117). The drug was subsequently shown to reduce disease exacerbations as a monotherapy in a Phase III trial (Ref. 118). Mitoxantrone suppresses T and B cells but is thought to have additional beneficial effects in MS patients, including induction of apoptosis in APCs and deactivation of macrophages, which are mediators of demyelination (Ref. 119). However, the drug has several potential side effects and its use is limited to a maximum of three years with current dosage, owing to the cardiotoxic effects at high cumulative doses. Thus, at the moment, it is used as a rescue treatment for patients not responding to IFN-β or GA, and to treat patients with very aggressive disease (Ref. 120).

The employment of statins, antihistamines, PPAR-α antagonists and angiotensin inhibitors to treat MS has several advantages. They are all widely used therapies, can be taken orally, have good safety records and are likely to be cost effective. These drugs all seem to have similar anti-inflammatory properties, and to polarise cytokine responses towards a Th2-type response (Ref. 121). Statins also reduce the expression of MHC class II and costimulatory molecules involved in T-cell activation (Ref. 121). All four drugs have been found to inhibit clinical aspects of EAE (Refs 121, 122, 123, 124). Statins have been found to reduce the formation of lesions in MS patients in small-scale trials (Ref. 125) and are now being subjected to larger-scale trials.

Conclusion and outlook

Therapeutic strategies in MS and other autoimmune diseases have always paralleled the current thinking on autoimmunity. For some time, the prevailing idea for a cure in autoimmune diseases has been to eradicate the immune cell clones responsible for the inflammatory attack and tissue damage. Accordingly, therapy has been aimed at eliminating or inhibiting these pathogenic cells, mainly through the use of immunosuppressive drugs, which affect every immune cell clone in the body. In recent years, it has become apparent that beneficial regulatory T cells are also inhibited by such a strategy, which is certainly not desirable, and may lead to a perpetuation of the autoimmune reaction. Thus, new approaches to treatment must be sought that specifically target the pathologically expanded, dangerous immune cell clones, yet sparing the regulatory T cells and exploiting their powerful ability to restrain autoaggressive T cells. The use of GA and other copolymers, APLs and TCV represent preliminary steps on the way to realising this ambitious goal. However, the greatest challenge in the development of these specific immunotherapies is to identify the target antigen(s) of the pathological immune response in MS. Thus far, the target structures and responding T-cell clones have not been identified with certainty, although there has been significant progress, as discussed above. New, large-scale approaches to identifying MHC associations, along with corresponding peptides and TCRs,

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might lead to a better understanding of what makes a T-cell clone pathogenic and might help to find potential points of intervention.

MS displays a great deal of clinical heterogeneity that reflects its diverse aetiology. It is possible, and indeed likely, that the pathological T-cell clones in each MS patient are highly variable. Ultimately, it seems that an individualised approach must be applied. Future techniques that can easily screen for the pathogenic clones and their target antigens in affected individuals must be developed to tailor potentially curative treatments to individual MS patients.

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Further reading, resources and contacts

An introduction to multiple sclerosis for medical students and physicians in training, created by members of the University of Utah School of Medicine and Kansas University Medical Center, hosts a series of lectures and training videos:
http://medstat.med.utah.edu/kw/ms/

Features associated with this article

Figures

Figure 1. The pathogenesis of multiple sclerosis (MS) and points of therapeutic intervention.
Figure 2. Molecular mimicry.

Table

Table 1. Major histocompatibility complex (MHC) associations in multiple sclerosis (MS).
Table 2. Important ongoing studies in the treatment of multiple sclerosis (MS).

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