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Animal models of multiple sclerosis—Potentials and limitations

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ABSTRACT

Experimental autoimmune encephalomyelitis (EAE) is still the most widely accepted animal model of multiple sclerosis (MS). Different types of EAE have been developed in order to investigate pathogenetic, clinical and therapeutic aspects of the heterogenic human disease. Generally, investigations in EAE are more suitable for the analysis of immunogenetic elements (major histocompatibility complex restriction and candidate risk genes) and for the study of histopathological features (inflammation, demyelination and degeneration) of the disease than for screening of new treatments. Recent studies in new EAE models, especially in transgenic ones, have in connection with new analytical techniques such as microarray assays provided a deeper insight into the pathogenic cellular and molecular mechanisms of EAE and potentially of MS. For example, it was possible to better delineate the role of soluble pro-inflammatory (tumor necrosis factor-α, interferon-γ and interleukins 1, 12 and 23), anti-inflammatory (transforming growth factor-β and interleukins 4, 10, 27 and 35) and neurotrophic factors (ciliary neurotrophic factor and brain-derived neurotrophic factor). Also, the regulatory and effector functions of distinct immune cell subpopulations such as $CD4^+$ Th1, Th2, Th3 and Th17 cells, $CD4^+FoxP3^+$ Treg cells, $CD8^+$ Tc1 and Tc2, B cells and $\gamma\delta^+$ T cells have been disclosed in more detail. The new insights may help to identify novel targets for the treatment of MS. However, translation of the experimental results into the clinical practice requires prudence and great caution.

Contents

Abbreviations: APC, antigen-presenting cell; AT-EAE, adoptive transfer EAE; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CD, cluster of differentiation; CNS, central nervous system; CNTF, ciliary neurotrophic factor; EAE, experimental autoimmune encephalomyelitis; HLA, human leukocyte antigen; Ig, immunoglobulin; IL, interleukin; IFN, interferon; IVIg, intravenous immunoglobulin; mAb, monoclonal antibody; MBP, myelin basic protein; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MP, methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; NK, natural killer; ODC, oligodendrocyte; QTL, quantitative trait locus; PLP, proteolipid protein; Tc, cytotoxic T cell; TCR, T cell receptor; TGF, transforming growth factor; Th cell, helper T cell; TNF, tumor necrosis factor.

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1. Introduction

1.1. Origins of EAE: from primates to rodents

Trials to investigate pathogenetic, diagnostic and therapeutic aspects of multiple sclerosis (MS) in animal models date back to the first half of the 20th century (Lindsey, 2005) (Fig. 1). Before, Louis Pasteur's rabies vaccination (Pasteur and Illo, 1996) gave first hints to the possibility that immunization of humans with xenogenic nervous tissue induces ascending paralysis. Specifically, inoculation of rabies patients with desiccated spinal cord of rabies-infected rabbits caused pareses of limb, neck and facial muscles resulting in gait, swallowing and breathing problems (Baxter, 2007). Conversely, it was shown by Koritschoner and Schweinburg (1925) and Stuart and Krikorian (1928) that injection of human spinal cord or sheep brain into rabbits leads to limb paralysis (clumsy gait and muscle weakness). Rivers et al. (1933) first demonstrated in monkeys immunized with rabbit brain or brain extracts that paralysis was associated with perivascular infiltrates and demyelination in the brain and spinal cord. He called the disease acute disseminated encephalomyelitis, a term that was later changed to experimental allergic or autoimmune encephalomyelitis (EAE). Since the frequency and severity of paralyses was correlated to the titer of anti-brain antibodies, researchers in subsequent trials boosted the humoral immune response with Freund's adjuvant (CFA) (Freund and McDermott, 1942), later complemented by pertussis toxin (Munoz et al., 1984). Thereby they could induce oscillatory symptoms and relapsing–remitting courses of the disease accompanied by perivascular leukocyte infiltration in acute lesions and gliosis in chronic lesions both reminiscent of MS pathology (Wolf et al., 1947). Experiments were performed first in guinea pigs (Freund et al., 1947) and monkeys (Kabat et al., 1947; Morgan, 1947; Wolf et al., 1947) and later in various other species including mice (Olitzky and Yager, 1949) and rats (Lipton and Freund, 1952) enabling more extensive immunogenetic, histopathological and therapeutic studies. It turned out that the histopathology and the clinical course of the disease varied significantly reflecting in part the heterogeneity of its human counterpart dependent on the genetic background of the animals, the source of the antigenic material and the mode of application of the antigen (Hartung et al., 2005; Olsson et al., 2000; Wekerle et al., 1994).

1.2. Different types of EAE

Importantly, by stepwise reduction of the complexity of the antigenic material from crude brain tissue and protein extracts through various central myelin proteins such as

(i) myelin basic protein (MBP) (Einstein et al., 1962; Laatsch et al., 1962),
(ii) myelin oligodendrocyte (ODC) glycoprotein (MOG) (Lebar et al., 1986),
(iii) proteolipid protein (PLP) (Tuohy et al., 1988),
(iv) myelin-associated oligodendrocytic basic protein and 2′,3′-cyclic nucleotide 3′-phosphodiesterase (Määttä et al., 1998)

to small encephalitogenic peptides (Eylar et al., 1970; Lennon et al., 1970) such as MBP_{1-37}, MBP_{1-11}, MBP_{1-9}, MBP_{83-99}, MOG_{55-75} and $PLP_{139-151}$, more reproducible EAE models became available that mirror different features of MS (Wekerle et al., 1994). More recently a variety of additional antigens have been supposed to be involved in autoimmune reaction in MS and EAE (Table 1). Some of them are myelin constituents such as neurofascin NF 155 (Mathey et al., 2007), others are expressed on myelin and axons such as contactin-2/transient axonal glycoprotein-1 (TAG-1) (Derfuss et al., 2009) and some are entirely non-myelin antigens such as the neuronal membrane protein neurofascin NF 186 (Mathey et al., 2007), the neuronal cytoskeletal protein neurofilament-M (Krishnamoorthy et al., 2009) and the astrocyte-typical Ca^{2+}-binding protein S100β (Kojima et al., 1997). The neurofascins NF 155 and NF 186 and the adhesion molecule contactin-2/TAG-1have been identified as putative MS auto-antigens by a proteomics-based screening approach of MS sera and were subsequently shown to promote the autoimmune pathogenesis of EAE in rat models (Derfuss et al., 2009, 2010; Mathey et al., 2007). Antibodies to neurofascins, in particular to NF 186, caused axonal injury without enhancing inflammation and demyelination in MOG–EAE (Mathey et al., 2007). In contrast to MOG–EAE, contactin-2/TAG-1-specific T cells induced inflammatory lesions preferentially in the cerebral cortex and the spinal cord white and gray matter (Derfuss et al., 2009). However, while these cells were unable to cause demyelination by themselves they opened the blood–brain barrier (BBB) thereby allowing access of anti-MOG antibodies to the central nervous system (CNS) where they could trigger demyelin-

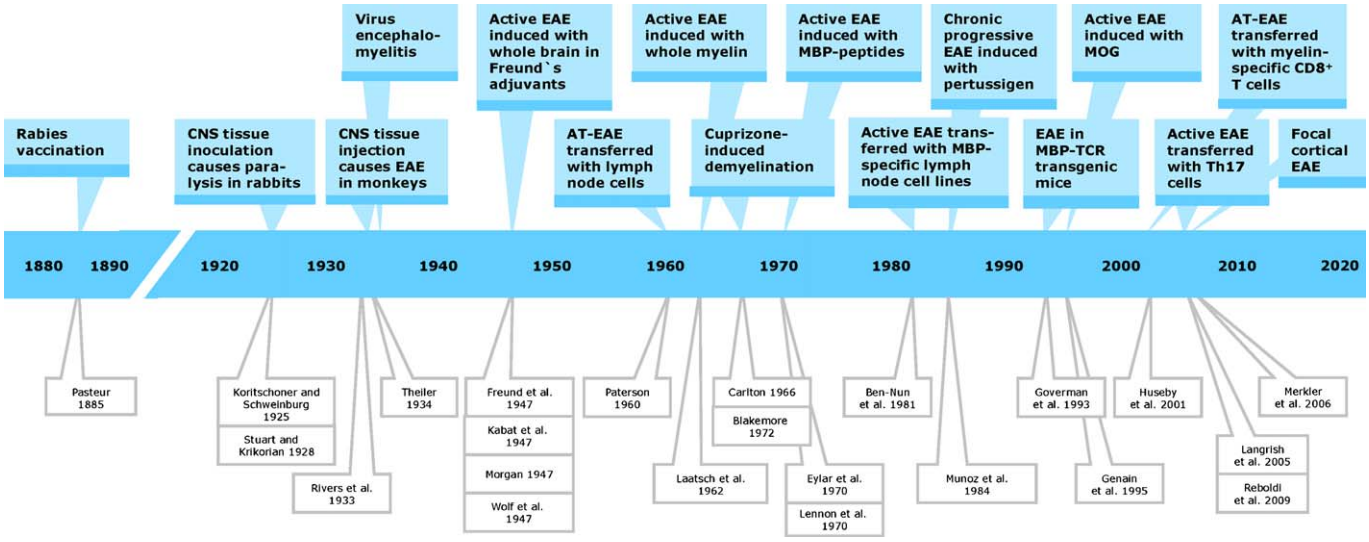


Fig. 1. Timeline of milestones in the history of animal models of MS. *Abbreviations*: AT-EAE, adoptive transfer EAE; CD, cluster of differentiation; CNS, central nervous system; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; TCR, T cell receptor; Th17 cell, interleukin-17 producing T helper cell.

Table 1
Putative protein and lipid auto-antigens in EAE and/or MS.

Antigens	Results in MS and/or EAE	References
Myelin basic protein	T and B cell response in EAE and MS	Einstein et al. (1962), Laatsch et al. (1962)
MOG	T and B cell response in EAE and MS	Lebar et al. (1986)
PLP	T and B cell response in EAE and MS	Tuohy et al. (1988)
2′,3′-CNP	T and B cell response in EAE and MS	Määttä et al. (1998)
NF 155	Antibodies recognize the extracellular domain in MS and cause axonal injury in EAE, but only in preexisting demyelinated lesions	Charles et al. (2002), Derfuss et al. (2010), Mathey et al. (2007)
NF 186	Antibodies recognize the extracellular domain in MS, inhibit axonal conduction in a complement-dependent manner and cause axonal injury in EAE	Derfuss et al. (2010), Hedstrom et al. (2007), Mathey et al. (2007)
Neurofilament-M	Neurofilament-M-specific T cells induce severe clinical EAE with confluent demyelination and massive axonal loss	Krishnamoorthy et al. (2009)
Contactin-2/TAG-1	Contactin-2/TAG-1-specific T cells induce inflammatory lesions in the cortex and white and gray matter thereby opening locally the BBB and causing occasionally clinical EAE	Derfuss et al. (2009, 2010), Mörtl et al. (2007), Shimoda and Watanabe (2009)
S100β	Strong T cell response in EAE	Kojima et al. (1997)
Phosphatidylserine	Promotion of demyelination in marmoset EAE	Ohler et al. (2004)
Sulfatides	T and B cell response in EAE	Kanter et al. (2006)
Oxidized phosphatidylcholine	Strong antibody reactivity in MS brain and EAE spinal cord	Qin et al. (2007)
Ganglioside GM1, sulfatide and galactosylceramide	Increased reactivity of pro-inflammatory cytokine secreting $CD8^+$ T cells in MS patients	Shamshiev et al. (1999)
Gangliosides GM3 and GQ1b	Increased T cell response in primary progressive MS patients	Pender et al. (2003)
Ganglioside GD1a	Increased antibodies in serum and cerebrospinal fluid of patients with MS and optic neuritis	Matà et al. (1999)
Lactosylceramide and L-α-lysophosphatidylserine	Strong antibody reactivity in serum and cerebrospinal fluid of MS patients	Kanter et al. (2006), Quintana et al. (2008b)

ation. The EAE variants induced by axonal antigens may reflect special features of MS subtypes, e.g. those characterized by cortical lesions or by histological patterns II and IV according to the classification of Lucchinetti et al. (2000). The schematic drawing in Fig. 2 indicates the molecular localisation of currently known putative auto-antigens in EAE. Proteins, glycoproteins and lipoproteins possessing encephalitogenic epitopes may be exposed to the outer surface of ODCs (1) or myelin (2) or they may reside in the compact myelin zone (3), at the myelin–axon interface (4) or the node of Ranvier (5). As to the last localisation the three adhesion molecules NF 155 and NF 186 contactin-2/TAG-1 are differentially expressed. Whereas NF 155 is localised at the paranodal myelin loop and interact with contactin-1/F3 and the contactin-associated protein 2 (caspr 2) on the axoplasm in a ternary complex (Charles et al., 2002), NF 186 is exposed in the non-myelinated part of the node of Ranvier and interacts with the neuron-glia-related cell adhesion molecule (NrCAM) and voltage-gated Na^+ channels (Hedstrom et al., 2007). Contactin-2/TAG-1 is also expressed juxtaparanodal by both the myelin and axonal membrane forming dimers or molecular zippers (Mörtl et al., 2007; Shimoda and Watanabe, 2009). Whether lipids, glycolipids and phospholipids play also a role as auto-antigens in EAE and MS is not clear, although several evidences from experimental and clinical studies support such a role (Podbielska and Hogan, 2009). Candiate myelin lipid auto-antigens in MS and/or EAE are shown in Table 1. In a lipid microarray study of Kanter et al. (2006) co-immunization with sulfatides and co-application of sulfatide-specific antibodies worsened the clinical course of $PLP_{139–151}$–EAE in SJL/J mice, and Quintana et al. (2008b) found auto-antibodies to lipids such as oxidized cholesterol derivatives in the serum of MS patients with the immunopathologic pattern II according to Lucchinetti et al. (2000). However, the oxidized cholesterol derivatives did not affect the specific humoral and T cell response in $MOG_{55–75}$–EAE.

Several studies have shown that actively induced EAE models can reproduce the typical temporal maturation of MS lesions from inflammation with or without deposition of immunoglobulin through demyelination and axonal damage to gliosis and partial remyelination. However, special phenotypes of MS pathology such as primary neuronal degeneration, shift of $CD4^+$ T helper cells to $CD8^+$ cytotoxic T cells and lesions in cortical areas are rarely reproduced by actively induced EAE models (Aktas et al., 2007; Gold et al., 2006; Herrero-Herranz et al., 2008; Linker et al., 2005; Pomeroy et al., 2005). Hitherto it is not clear to which extent cortical lesions account for the brain atrophy in MS. Merkler et al. (2006) could induce focal demyelinating lesions in the cortex of MOG–EAE rats by stereotactical injection of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). Corresponding to findings in MS the focal cortical lesions were rapidly remyelinated. Accordingly, in marmoset MOG–EAE focal cortical lesions were not the major cause of diffuse cortical atrophy (Pomeroy et al., 2008). The potential pathomechanisms of CNS atrophy in MS are complex and may include several mechanisms of neuronal damage such as anterograde Wallerian degeneration, neuronal dying-back and neuronal soma and dendritic shrinkage (Dziedzic et al., 2010; Siffrin et al., 2010). Currently, disclosure of the exact mechanisms of axon damage is a major challenge of MS research, since it appears to be the main cause of clinical disability and may be the result of immune and/or non-immune attacks on neurons rather than a consequence of immune-mediated demyelination (Siffrin et al., 2010).

Concerning the aetiopathogenesis of MS the role of infections is still a matter of controversy. In mice lymphocytic choriomenigitis virus protein expression could elicit chronic autoimmune inflammation and demyelination in the CNS (Evans et al., 1996). A *Chlamydia pneumonia*-specific peptide sharing an immunodominant epitope with MBP-induced severe clinical and histological EAE (Lenz et al., 2001), whereas intestinal parasites conveyed resistance to EAE in EAE-susceptible Lewis rats (Zorzella et al., 2007). Also, human herpes virus type 6, Epstein–Barr virus, measles virus and retroviruses have been implicated in the aetiopathogenesis of MS, but currently available experimental and clinical data are not convincing enough to justify anti-viral or antibiotic therapy in MS. However, experimental demyelinating diseases induced by Theiler's virus (Theiler, 1934; Ure and Rodriguez, 2005), coronavirus (Lavi, 2005) or canine distemper virus (Seehusen and Baumgärtner, 2010) are suitable models for the investigation of some aspects of MS pathology.

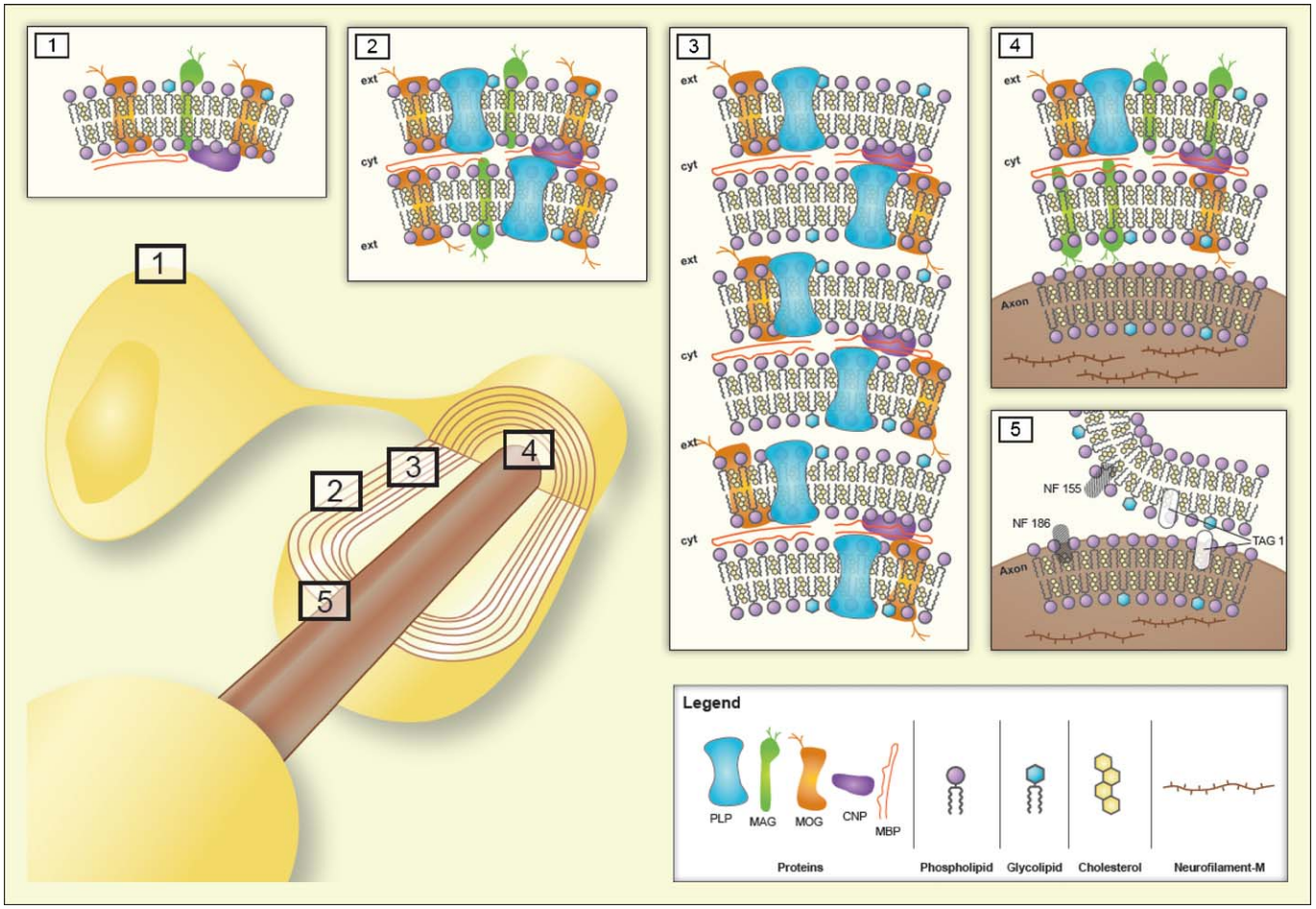


Fig. 2. Putative auto-antigens in EAE with indication of their preferential localisation. Insets refer to the ODC membrane (inset 1), myelin surface zone (inset 2), compact myelin zone (inset 3), myelin/axon interface zone (inset 4), and nodal and paranodal zone of node of Ranvier (inset 5). *Abbreviations*: CNP, 2′,3′-cyclic nucleotide-3′-phosphodiesterase; cyt, cytoplasm; ext, extracellular space; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; NF, neurofascin; PLP, proteolipid protein; TAG, transient axonal glycoprotein.

Milestones of the development of increasingly specific EAE models were (Fig. 1):

(i) Induction of EAE by transfer of total lymph node cells (Paterson, 1960), isolated MBP-specific T cell-line cells (Ben-Nun et al., 1981) or interleukin-23 (IL-23)-dependent PLP-specific $CD4^+$ T helper IL-17 (Th17) cells (Langrish et al., 2005) into naive rats or mice, respectively, establishing distinct forms of adoptive transfer EAE (AT-EAE) and

(ii) generation of transgenic mice with deletion (knock-out leading to loss-of-function) or over-expression (knock-in leading to gain of function) of pathogenetically relevant genes (reviewed in Krishnamoorthy et al., 2007). Examples of such genes are those encoding T cell receptors (TCRs) (Bettelli et al., 2006; Goverman et al., 1993; Lafaille et al., 1994; Mendel et al., 2004), major histocompatibility complex (MHC) molecules (Friese et al., 2008; Khare et al., 2005; Linker et al., 2005; Mangalam et al., 2008), cytokines (reviewed in Campbell et al., 1998; Owens et al., 2001) as well as neurotrophic factors (Linker et al., 2005, 2008a, 2009b; Mirowska-Guzel, 2009) and their receptors (Dallenga et al., 2009; Linker et al., 2009b).

The constitutive knock-out or knock-in of cytokine genes throughout the whole development and adulthood of an animal implies serious drawbacks due to redundancy and feed-back loops of cytokine signal pathways (Owens et al., 2001; Steinman, 1997). This constraint can been overcome by approaches with inducible spatially and temporally restricted gene targeting, which has been only recently introduced for studies directed to the CNS (Gavériaux-Ruff and Kieffer, 2007; Hövelmeyer et al., 2005).

Despite the obvious importance of autoimmune processes in the pathogenesis of MS, there is evidence for a non-immune origin of at least some subtypes of MS. For example, even aggressive immunosuppression is not sufficient to treat progressive MS. Therefore, additional experimental models are needed, especially for the study of non-immune-mediated demyelination and axonal loss via ODC degeneration. For this purpose a toxic model of demyelination has been developed that is based on the selective toxicity for ODCs of the copper chelator biscyclohexanone oxaldihydrazone (cuprizone) (Blakemore, 1972; Carlton, 1966). If young mice are fed with cuprizone, focal demyelination occurs predominantly in the cerebellar cortex and peduncle. After withdrawal of the toxin spontaneous remyelination can be seen predominantly in the rostral regions (Skripuletz et al., 2010; Torkildsen et al., 2008). Thereby the cuprizone-model correlates well with histopathological features of MS, especially in the subtype or variant classified as histological pattern III according to Lucchinetti et al. (2000), which renders it a useful tool for MS research (Einstein et al., 2009; Kipp et al., 2009). Paradoxically, according to a recent report of Herder et al. (2009) cuprizone ameliorates Theiler's murine encephalomyelitis suggesting that it might have immunomodulatory and/or anti-viral properties in addition to its toxic effects.

1.3. Current EAE models

Currently, the most common mode of EAE induction is based on the injection of an encephalitogenic peptide, mostly MOG_{35-55} or $PLP_{139-151}$, which is emulsified in CFA containing mineral oil and *Mycobacterium tuberculosis* strain H37RA, followed by intraperitoneal injections of pertussis toxin (Fig. 3). The resulting phenotype depends mainly on the antigen source and the genetic background of the animal species and strains used. For example, $PLP_{139-151}$ induces a relapsing–remitting EAE in SJL mice, whereas MOG_{35-55} triggers chronic-progressive EAE in C57BL mice that are the most favored mice for transgenic experiments (Gold et al., 2006). Crossing of C57BL mice, which over-express MOG-TCR and MOG-specific B cells, resulted in a severe form of EAE that closely replicated Devic's variant of MS with inflammatory lesions of optic nerves and spinal cord (Bettelli et al., 2006). MOG-TCR transgenic mice backcrossed to SJL/J background develop a relapsing–remitting form of EAE with episodes altering between optic nerve, cerebellum and spinal cord. Evolution of this model depends on an intact B cell compartment. Apparently, MOG-TCR transgenic T cells expand endogenous auto-reactive B cells that manufacture pathogenic demyelinating auto-antibodies to a conformational epitope on native MOG protein whilst not recognizing the T cell target MOG peptide (Pöllinger et al., 2009). The authors claim to have generated the first spontaneous animal model for relapsing–remitting MS. Current types of AT-EAE include those induced by Th17 cells suggesting that these newly detected effector cells may in part be responsible for the pathological heterogeneity of MS lesions (Afzali et al., 2007; Gold and Lühder, 2008; Hofstetter et al., 2007, 2009; Jäger et al., 2009; Korn et al., 2007; Quintana et al., 2008a; Reboldi et al., 2009). All EAE models are directly accessible to investigation of the immune and nervous system (Fig. 3), which interact during the pathogenesis of the disease and which are both targeted by established and experimental therapies.

2. Investigation of immunogenetic and pathogenetic features

2.1. Immunogenetics of EAE and MS

Since MS appears to be a polygenetically determined disease, efforts have been undertaken by linkage and association studies to define chromosomal regions, quantitative trait loci (QTL), that control the susceptibility to the disease and to compare these QTL with the susceptibility loci in the animal model EAE (Serrano-Fernández et al., 2004). The high frequency of intergenomic EAE/MS consensus genes supports the value of EAE for studying of MS features. Backcross (offspring-parent mating) and intercross (sibling mating) experiments with EAE susceptible and resistant animal strains of mice, rats, guinea pigs and hamsters revealed mainly MHC-linked QTL (Encinas et al., 1996; Olsson et al., 2000). Combined-cross analysis could enhance the detection of QTL with moderate effects in rats (Jagodic and Olsson, 2006). Genotyping of 150 microsatellite markers in F2 intercross populations of EAE-susceptible SJL/L mice and EAE-resistant C57BL/10.S mice identified QTL linked to increased latency of cortical motor evoked potentials in non-immunized animals, which correlated with earlier onset of the disease (Mazón Peláez et al., 2005). This finding points to a role of myelin composition and synaptic transmission in susceptibility to EAE and provides a chance to detect individuals with high risk for autoimmune demyelination by QTL analysis before the disease is manifested. In MS, some immune response-related genes have been identified by genome-wide association studies using single nucleotide polymorphism analysis with microarray technique as being heritable risk factors of the disease, although their individual contribution is clearly modest with odds ratios for most not exceeding 1.2 (IMSGC, 2007). These genes include the interleukin (IL)-2α and IL-7α receptor genes on chromosomes 10 and 5, respectively, and some human leukocyte antigens (HLA) belonging to MHC class II molecules on chromosome 6 (Table 2) (Gregory et al., 2007; IMSGC, 2007). More recently, the genes encoding the following proteins have been confirmed as novel MS risk genes (explanation of abbreviations in Table 2) (Aulchenko et al., 2008; Dabbeekeh et al., 2007; De Jager et al., 2009a,b; Hafler et al., 2009; Hoppenbrouwers et al., 2008, 2009; IMSGC, 2007; Johnson et al., 2010; Mero et al., 2010; Rubio et al., 2008; Sarrias et al., 2007):

- EV15, CD58, KIF1B, RGS1 and RPL5 (on chromosome 1),
- IL-12A (on chromosome 3),
- PTGER4 (on chromosome 5),
- OLIG3-TNFAIP3 (on chromosome 6),
- CD6 (on chromosome 11),
- TNFRSF1A (on chromosome 12),
- IRF8 and CLEC16A (on chromosome 16),
- CD226 (on chromosome 18), and
- TYK2 (on chromosome 19).

The strongest association to MS susceptibility, although not to the age of onset and severity of the disease, was found for the HLA-DRB1*1501 allel (Barcellos et al., 2006; Chao et al., 2008), whereas transgenic mice over-expressing the human HLA-DRB1*1502 allel developed a severe MOG–EAE (Khare et al., 2005). In contrast, genes related to antigen processing can also slow down disease progression as reflected by a milder course of the disease in MOG_{35-55}–EAE of congenic NOR/LtJ mice compared to the wild-type NOD mice (Mayo and Quinn, 2007). Similarly, congenic mapping of the rat genome confirmed that a chromosomal region homologous to a human MS susceptibility region confers protection against MOG–EAE (Jagodic et al., 2001). Also, transgenic MOG_{35-55}–EAE mice over-expressing the TCR for MOG_{35-55} showed protective rather than pathogenic effects (Mendel et al., 2004). In contrast, transgenic mice over-expressing MBP-specific TCR developed high frequency spontaneous EAE (Goverman et al., 1993; Lafaille et al., 1994). The relevance of these findings for the human disease remains to be elucidated. Research in EAE also yielded hints for the existence of chromosomal loci that control disease susceptibility in dependence of age and season pointing to a role of chronobiology in autoimmunity (Teuscher et al., 2006). Moreover, EAE susceptibility can vary even between different colonies of the same animal strain

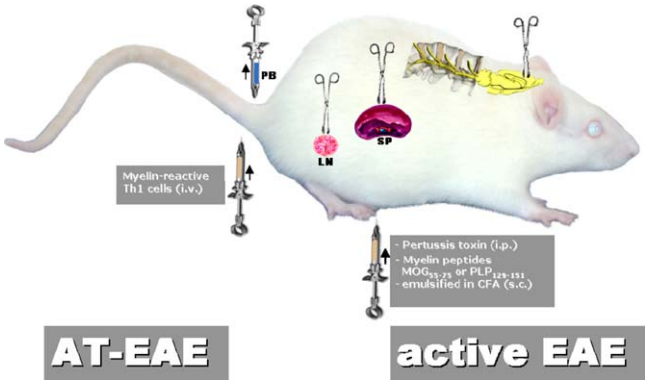


Fig. 3. Most common animal models of MS with indication of the compartments investigated for analysis of systemic and local disease processes. For active immunization antigens are preferentially applied to the flank or toe pad of the animal, since draining lymph nodes of these areas mediate a highly effective systemic immune response to the putative auto-antigens as a first step for induction of autoimmune processes in the CNS. *Abbreviations*: AT-EAE, adoptive transfer EAE; CFA, complete Freund's adjuvant; i.p., intraperitoneal; i.v., intravenous; LN, lymph node; MOG, myelin oligodendrocyte glycoprotein; PB, peripheral blood; PLP, proteolipid protein; s.c., subcutaneous; SP, spleen, Th1 cells, T helper type 1 cells.

Table 2
Susceptibility genes of MS.

Gene	Function	References
HLA-DRB1*1501	Antigen presentation	Barcellos et al. (2006), Chao et al. (2008), IMSGC (2007), Khare et al. (2005)
IL-2α receptor	T and B cell activation	IMSGC (2007)
IL-7α receptor	T cell survival, differentiation and homeostasis, B cell development	Gregory et al. (2007), IMSGC (2007)
EV15	GTPase activation	Dabbeekeh et al. (2007), Hoppenbrouwers et al. (2008)
CD58 (lymphocyte-associated antigen 3, LFA-3)	Ligand of CD2, costimulatory molecule for T cells enhancing FoxP3 expression in Treg cells	De Jager et al. (2009a), Hoppenbrouwers et al. (2009)
CLEC16A (C-type lectin domain family 16, member A)	Unknown function, but highly expressed in dendritic cells, B cells and NK cells...	Hoppenbrouwers et al. (2009), Johnson et al. (2010), Rubio et al. (2008)
CD6	Bacterial molecular pattern recognition and suppressing TNF-α, IL-6 and IL-1β	De Jager et al. (2009b), Sarrias et al. (2007)
IRF8 (IFN regulatory factor 8)	Activation or repressing of IFN type I transcription	De Jager et al. (2009b), Johnson et al. (2010)
TNFRSF1A (tumor necrosis factor receptor superfamily, member 1A)	Pro-inflammatory and proapoptotic activity	De Jager et al. (2009b)
OLIG3-TNFAIP3 (oligodendrocyte transcription factor 3—NF-α-induced protein 3)	Development of neuronal cells, tumor suppression and anti-inflammation	De Jager et al. (2009b)
IL-12A (IL-12p35)	Growth factor for activated T and NK cells, enhancing the lytic activity of NK/lymphokine-activated killer cells	Rubio et al. (2008)
PTGER4 (prostaglandin E receptor 4)	Activation of T cell factor signaling	De Jager et al. (2009b)
RGS1 (regulator of G-protein signaling 1)	B cell activation	Johnson et al. (2010)
TYK-2 (tyrosine kinase 2)	Intracellular signal transduction of type I IFNs	Johnson et al. (2010), Mero et al. (2010)
CD226	Intercellular adhesion, lymphocyte signaling, cytotoxicity and lymphokine secretion mediated by cytotoxic T cells and NK cells	Hafler et al. (2009)
KIF1B (kinesin family member 1B)	Motor protein transporting mitochondria and synaptic vesicle precursors	Aulchenko et al. (2008)
RPL5 (ribosomal protein L5)	Transport of nonribosome-associated cytoplasmic 5S rRNA to the nucleolus for assembly into ribosomes.	Rubio et al. (2008)

as demonstrated for Lewis rats purchased from different animal facilities (Gould et al., 1994). Since the genetic background of these animals is almost identical, other mechanisms, preferentially those involving gene regulating, may be responsible for differences in disease susceptibility and progression. Transcriptome and proteome analyses are powerful new tools for the elucidation of those mechanisms (Elkabes and Li, 2007; Fernald et al., 2005; Goertsches and Zettl, 2007; Ibrahim et al., 2001; Ibrahim and Gold, 2005).

2.2. Gene expression studies by microarray analysis

An integrated analysis of available data from genome-wide genetic screens and high-throughput gene expression studies in MS and EAE revealed that differentially expressed genes appear mainly in clusters rather than in uniform distribution throughout the genome (Fernald et al., 2005). The hereby included hypothesis-neutral gene expression studies are mainly performed with microarray technique (RNA profiling) and applied in MS patients to peripheral blood mononuclear cells or brain tissue and in EAE animals to lymphatic and nervous tissue (Goertsches and Zettl, 2007; Tajouri et al., 2007). They deliver an increasing wealth of data, which implies a great challenge for bioinformatic analysis that may include pathway analyses using background information from the Gene Ontology project and other data bases as well as data mining approaches. Results of gene expression studies are generally hampered by methodical problems such as the heterogeneity of the material from different individuals and the difficulties in defining a reasonable threshold for differentially expressed genes. Nevertheless, meaningful data have already been obtained from expression studies in EAE that point to new EAE-QTL and susceptibility genes, dissect new pathogenic and protective pathways and identify new therapeutic targets (Comabella and Martin, 2007; Jelinsky et al., 2005; Matejuk et al., 2003; Mazón Peláez et al., 2005; Mix et al., 2002, 2006; Paintlia et al., 2004). As an example, the comparison of the EAE-resistant strain C57BL/10.S with the EAE-susceptible strain C57BL/6 in the MOG_{35-55}–EAE model strongly supported EAE-resistance to be an active process revealing new target genes for therapeutic intervention (Mix et al., 2004). Moreover, data of Baranzini et al. (2005) derived from the MOG_{35-55}–EAE model led to new conclusions such as

(i) early non-specific BBB impairment (mainly neutrophil-related) secondary to immunization with CFA,
(ii) transition from innate to adaptive immune responses before onset of EAE,
(iii) identification of at least 3 discrete EAE phases (early EAE, peak EAE and early recovery) with characteristic gene expression patterns, and
(iv) early neuronal damage.

Therefore, gene expression studies can provide new insights into the dynamics of discrete early and progressive phases of EAE on the transcriptional level, which are consistent with the histological and clinical phenotype. They can serve as a tool for fingerprinting of individual disease processes in man. As a practical consequence new therapeutic targets surface. RNA profiling has also enabled researchers to identify genes which support maintenance of the hematopoietic stem cell niche synapse as a source for therapeutic mesenchymal stem cells that can ameliorate EAE (Pedemonte et al., 2007). On the other hand, EAE can also serve as a tool to validate new targets derived from gene-microarray analysis (Lock et al., 2002).

Despite the clear benefit of the transcriptome approach there are voices advising caution concerning overinterpretation of results of global gene expression analysis. In any case, due to its obvious limitations transcriptomics should be employed only with a clear and specific question in mind and carefully in view of the regulatory settings and potential pitfalls of the technique (Casciano and Woodcock, 2006; Fathallah-Shaykh, 2005). The same is true for the proteome approach (reviewed in Elkabes and Li, 2007; Linker et al., 2009a). In EAE, it has served to generate differential protein

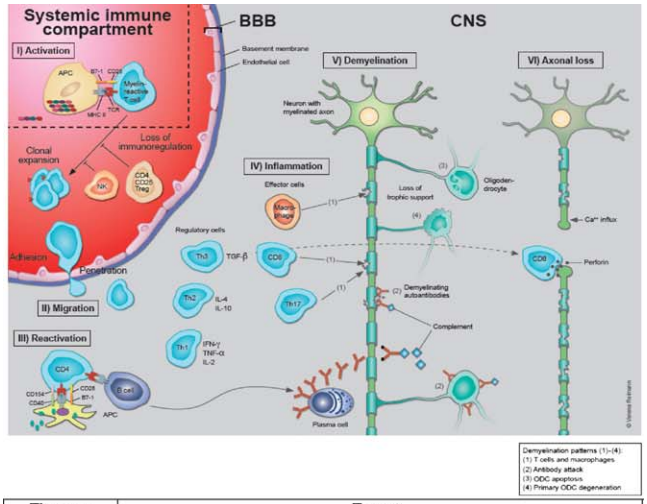
expression profiles (Duzhak et al., 2003; Liu et al., 2007), to monitor the diversity of autoantibody responses (Robinson et al., 2003) and to validate new therapeutic targets derived from laser-capture micro-dissections of MS lesions (Han et al., 2008). Also putative lipid auto-antigens could be identified by the microarray approach in MS and EAE (Kanter et al., 2006; Quintana et al., 2008b).

2.3. Immunopathogenesis

There is still consensus amongst most researchers that immunological processes play a pivotal role in the pathogenesis and progression of MS (Gold et al., 2006; Linker et al., 2008c; Steinman and Zamvil, 2006; Weiner, 2009), although the aetiological factors may vary between different subtypes of MS and may not primarily affect the immune system, especially in cases with the histopathologic patterns III and IV according to Lucchinetti et al. (2000). Moreover, in early MS with histologic patterns I–III Wallerian degeneration seems to contribute significantly to axonal loss in the plaques and periplaque white matter (Dziedzic et al., 2010). The current concept of pathogenetic processes in MS is schematically depicted in Fig. 4, which indicates also therapeutic interventions and their putative targets. Recent paradigm shifts relate to the recognition of new roles for $CD8^+$ T cells (Friese and Fugger, 2009), B cells (Franciotta et al., 2008), innate immunity (Weiner, 2009) and emerging pathogenic pathways causing neuronal damage (Aktas et al., 2010; Centonze et al., 2010; Dziedzic et al., 2010; Herz et al., 2009).

EAE models have considerably contributed to our understanding of immune regulatory processes in the pathogenesis of MS (Gold et al., 2006; Wekerle et al., 1994). While traditionally regulatory (suppressive) activity in autoimmune processes was primarily attributed to $CD8^+$ T cells (Zozulya and Wiendl, 2008), more recently $CD4^+CD25^+FoxP3^+$ regulatory T cells (Yi et al., 2006) have attracted interest in this respect (Ephrem et al., 2008; Paintlia et al., 2008; Tischner et al., 2006). They seem to be important as antagonists of $CD4^+$ Th17 cells (Afzali et al., 2007; Littman and Rudensky, 2010; Quintana et al., 2008a) that are supposed to be effector cells in EAE (Hofstetter et al., 2007; Huppert et al., 2010; Liu et al., 2010; Steinman, 2007) and MS (Gold and Lühder, 2008). However, the pathogenic role of Th17 cells and of IL-17 in EAE is controversial. According to findings of Haak et al. (2009) in transgenic mice the *in vivo* function of IL-17 in the CNS may be redundant and the members of the IL-17 family IL-17A and IL-17F may contribute only marginally to the autoimmune pathogenesis of MOG_{35-55}–EAE. On the other hand, Huppert et al. (2010) found that IL-17A promotes breakdown of the BBB, a crucial step in the development of EAE. Moreover, findings of Nowak et al. (2009) point to a pro-inflammatory role of the Th17-derived IL-9 in MOG_{35-55}–EAE. Th17 cells are driven by IL-21 (Korn et al., 2007) and IL-23 (Langrish et al., 2005; McKenzie et al., 2006) and suppressed by IL-27 (Fitzgerald et al., 2007; Wang et al., 2008). Recently, the IL-7-IL-7R pathway has been implicated in the survival and expansion of effector/memory Th17 cells. Blockade of IL-7R rendered differentiated Th17 cells susceptible to apoptosis which led to attenuation of MOG–EAE (Liu et al., 2010). Corresponding IL-17^+ $CD8^+$ Tc cells show impaired cytotoxicity and IFN-γ production, but may through their excessive IL-17 production contribute to inflammatory processes in EAE and MS (Huber et al., 2009). Recently, Sobottka et al. (2009) could demonstrate in brain slices of transgenic mice that myelin-directed $CD8^+$ Tc cells cause extensive damage not only of the myelin sheath, but also of the axons. Consequently, these cells may contribute to axonal loss in EAE and probably also in MS with the immunopathologic pattern I according to Lucchinetti et al. (2000).

B cells are involved in the immunopathogenesis of MS and EAE at least by two functional activities, i.e. as antigen-presenting cells



Therapy	Target						
	Activation	Migration	Reactivation	Inflammation	Demyelination	Axonal loss	Clonal expansion
Successful translation into the clinic							
Glatiramer acetate	X		X				
Mitoxantrone	X		X				X
Natalizumab		X					
Failure of translation into the clinic							
Anti-TNFα				X	X		
Anti-CD3/4	X		X				X
Anti-CD28 (TGN-1412)	X		X				
APL			X				
Oral tolerogens			X				
Sulfalazine				X			
Linomide				X			
Anti-CD54		X					
Phenytoin						X	
CNTF					X	X	
Currently tested in clinical studies and/or EAE							
IL-4 gene therapy	X		X				
Stem cells (MSC, NSC)				X	X	X	
Neurotrophic factors (BDNF, EPO)					X	X	
CRYAB				X			
Ceftriaxone	X	X	X				
Corticosteroids		X		X			
Statins	X	X					
Fingolimod (FTY720)	X				X		
Fumarate (BG-12)				X		X	
Minocycline		X					
PPARα-agonists				X			
Laquinimod				X			
AICAR				X			
CYLA		X			X	X	
3,4-DAA				X			
EGCG				X	X		X
Flavonoids		X		X			
Metallothionein				X		X	
Vitamin D		X	X				
K⁺-channel blocker	X		X				
Lamotrigine						X	
DRD1 antagonists					X		
Glutamate receptor antagonists					X	X	
Histamin receptor antagonists				X			
SSRI				X			
CD11a-PLP-hybrid	X		X				
Fulleren hybrid (ABS-75)		X			X	X	
Rituximab	X		X				
Daclizumab	X		X				X
Alemtuzumab	X		X				X
Teriflunomide	X		X				X
Temsirolismus	X		X				X
Cladribine	X		X				X
Vaccine	X		X	X			

Fig. 4. Putative pathogenic mechanisms of MS. Auto-reactive lymphocytes may be recruited from peripheral lymphoid organs and after migration through the BBB reactivated in the CNS, where an inflammatory cascade is initiated leading to subsequent damage of myelin and axons. Alternatively, primary oligodendroglial and axonal degeneration may be followed by an inflammatory autoimmune process. The adjacent table depicts the putative pathogenic processes that are targeted by established and experimental therapies. Treatments are grouped according to the contribution made by EAE to their development, i.e. they are either successfully translated into the clinic (green), only successful in EAE (red) or currently tested in EAE and/or MS (yellow). *Abbreviations*: AICAR, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside; APC, antigen-presenting cell; APL, altered peptide ligand; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CD, cluster of differentiation; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CRYAB, αB-crystallin; CYLA, Calpain inhibitor; 3,4-DAA, N-(3,4,-dimethoxycinnamoyl) anthranilic acid; DRD1, dopamine receptor type 1; EGCG, (−)-epigallocatechin-3-gallate; IL, interleukin; IFN-γ, interferon-γ; major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MP, methylprednisolone; MRI, magnetic resonance imaging; NK, natural killer; ODC; oligodendrocyte; PLP, proteolipid protein; PPAR-α, peroxisome proliferator-activated receptor-α; SSRI, selective serotonin reuptake inhibitor; Tc, cytotoxic T cell; TCR, T cell receptor; TGF-β, transforming growth factor-β; Th cell, helper T cell; TNF-α, tumor necrosis factor-α.

(APCs) and as antibody producers (Franciotta et al., 2008; Goverman, 2009; Hohlfeld et al., 2008; Martin Mdel and Monson, 2007; Weiner, 2009; Ziemssen and Ziemssen, 2005). In addition they may co-stimulate T cells, facilitate recruitment of inflammatory cells to the CNS and myelin opsonization, but also promote remyelination, and take part in immunoregulatory processes. Antimyelin antibodies are supposed to be major components of the histopathologic MS pattern II according to Lucchinetti et al. (2000). A special role as targets for antibodies in distinct types of EAE and MS is ascribed to the myelin molecules MOG (Haase et al., 2001) and the axonal molecule neurofascin (Hohlfeld et al., 2008).

Another distinct lymphocyte subpopulation that has been implicated in CNS autoimmunity is the $\gamma\delta^+$ T cell subset bearing TCR$\gamma\delta$. These fetal-type T cells are increased in number in MS cerebrospinal fluid (Mix et al., 1990) and may exert pathogenic and regulatory functions (reviewed in Blink and Miller, 2009 and Goverman, 2009). Interestingly, the majority of IL-17 producing host cells in a Th1-mediated AT-EAE belonged to the $\gamma\delta^+$ T cell type (Lees et al., 2008).

Adding to the complexity, there is an obvious pathogenic role for EAE and MS of innate immunity mediated by dendritic cells, monocytes and microglia (Furtado et al., 2006). Whereas the adaptive immune system seems to drive mainly relapses of MS, abnormalities of the innate immune system may prevail in the progressive stage of the disease (Weiner, 2009).

An important aspect of MS pathogenesis is the apoptotic activity in the lymphatic and nervous system. Therefore, apoptotic processes have been analysed in EAE. While apoptosis plays obviously a pivotal pathogenic role when affecting ODCs (Hövelmeyer et al., 2005), it appears to be protective when eliminating myelin-reactive and bystander T cells (Zettl et al., 1997). This process is augmented by therapeutic drugs such as methylprednisolone (MP) (Schmidt et al., 2000) and resveratrol (Singh et al., 2007).

The role of cytokines and neurotrophic factors for the pathogenesis of MS and EAE has been investigated in a plethora of studies and the results have been reviewed elsewhere (Goverman, 2009; Imitola et al., 2005; Link, 1998; Linker et al., 2009b; Mirowska-Guzel, 2009; Owens et al., 2001; Ozenci et al., 2002). For details the reader is referred to these reviews.

In addition to the mentioned immunopathogenic pathways a direct crosstalk between the immune and nervous system may influence the pathogenesis of MS and EAE (Kerschensteiner et al., 2009; Mix et al., 2007). This involves direct effects of cytokines and chemokines on nerve cells and modulation of immune cell activity by neurotrophins and neurotransmitters implicating new treatment approaches, e.g. by associative conditioning (Jones et al., 2008). Disclosure of the complex mechanisms of neuro-immune interactions requires further investigations in the EAE model.

Many other aspects of MS research are investigated in the animal model. Among them monitoring of disease activity by traditional magnetic resonance imaging (MRI) (Morrissey et al., 1996) and new bioluminescence techniques (Luo et al., 2008) deserve special attention. Identification of reliable surrogate markers for diagnostic and prognostic purposes (responder detection for specific therapies, disease follow-up) will be a prominent task of the future. However, a consistent limitation for the translation of experimental results into the clinic is the different situation in EAE and MS concerning the timeline of detection of clinical signs and of therapeutic interventions (Fig. 5). Whereas in EAE pathological processes can be observed from the beginning and treatment approaches can be started at the early pre-clinical phase, in MS diagnostic measures will commonly not be initiated before first clinical signs are present and the intensity of treatment increases usually until late progression of the disease.

3. Development and validation of novel therapies

3.1. Therapies developed primarily in EAE

Despite extensive screening for new targets of MS therapy in EAE so far only a few of the established MS therapies have been developed in the animal model. Examples are glatiramer acetate, mitoxantrone and natalizumab (Kieseier and Hartung, 2003; Steinman and Zamvil, 2006).

The glatiramer acetate preparation is a random polymer consisting of repeated sequences of the four amino acids glutamic acid, lysine, alanine and tyrosine that occur in MBP in a specific molar ratio. It was primarily called copolymer 1 and tested first for its encephalitogenic potency and subsequently for its influence on guinea pig EAE (Teitelbaum et al., 1971). Surprisingly, it turned out that copolymer 1 suppressed rather than induced EAE, most probably via stimulation of Th2/Th3-mediated anti-MBP immune response (Aharoni et al., 1997, 2008). Recent studies utilising sophisticated immunologic techniques point to a more complex mechanism of action of glatiramer acetate, including modification and killing of APCs, generation of regulatory T cells and turning the polyclonal $CD8^+$ T cell response into an oligoclonal one (Racke et al., 2010).

Mitoxantrone has first been proven to be a powerful immunosuppressive drug in EAE (Ridge et al., 1985) and it is now a second-line component of escalating MS therapy (Hartung et al., 2002; Krapf et al., 2005; Neuhaus et al., 2006a,b; Rieckmann et al., 2004). Its mechanism of action relies most probably on

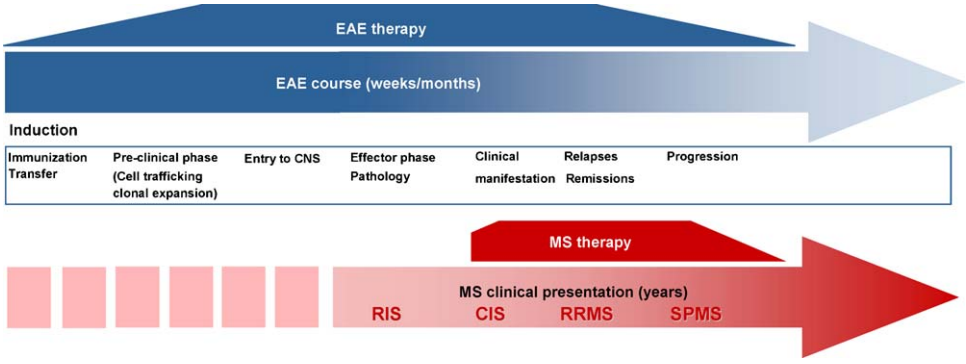


Fig. 5. Timeline of the pathophysiological and clinical course of EAE and MS. In EAE, the complete pathological course including the pre-clinical phase is detected and immune therapeutic interventions start early and decrease usually with the proceeding time. In MS, there is an opposite situation. First radiological signs remain usually undetected and immunomodulatory treatment starts only with first clinical signs and is usually intensified until late progression of the disease. *Abbreviations*: CIS, clinical isolated syndrome; CNS, central nervous system; RIS, radiologic isolated syndrome; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.

cytotoxic effects on lymphocytes and induction of apoptosis of APC such as monocytes and dendritic cells (Neuhaus et al., 2005; Vollmer et al., 2010).

Natalizumab is a monoclonal antibody (mAb) that inhibits the transmigration of immune cells into the inflamed parenchyma of lymphatic organs and the CNS. It binds to α4β1-integrin (CD49dCD29, very late activation antigen-4) on lymphocytes and blocks the interaction with the integrin ligand CD106 (vascular cell adhesion molecule-1) on endothelia cells thereby being effective in preventing EAE (Rice et al., 2005; Yednock et al., 1992). It is the first mAb approved for therapeutic trials in MS (Polman et al., 2006) now belonging to second-line MS therapeutics, although it carries the risk to activate the polyoma virus JC leading to progressive multifocal leukoencephalopathy, especially if applied in combination with IFN-β (Clifford et al., 2010; Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005; Stüve and Bennett, 2007; Yousry et al., 2006). Recently, even cases of progressive multifocal leukoencephalopathy on natalizumab monotherapy have been reported (Clifford et al., 2010; Hartung, 2009; Hartung et al., 2009; Lindå et al., 2009; Wenning et al., 2009).

3.2. Therapies investigated secondarily in EAE

A number of established MS therapies have subsequently been investigated in the EAE model. The aims are:

(i) to get a deeper insight into the mechanisms of action including disclosure of the specific targets of the therapies and
(ii) to improve regimens of old therapies and to develop new therapies targeting the same pathogenic mechanisms, but being more convenient for clinical practice (low frequency of application, oral application) and avoiding adverse side-effects.

For example, with respect to methylprednisolone therapy for MS relapses Schmidt et al. (2000) could unravel a switch from cytoplasmic to nuclear effects accompanied by enhanced T cell apoptosis with increasing steroid dosage. Moreover, liposome encapsulated MP revealed a dose-dependently increased therapeutic efficiency compared to free MP in EAE (Linker et al., 2008b). In IFN-β treated EAE, interruption of therapy caused disease exacerbation (van der Meide et al., 1998). In an attempt to explore the influence of intravenous immunoglobulin (IVIg) therapy on the local immune response in the CNS, Jørgensen et al. (2007) found accumulation of IVIg only in active CNS lesions with BBB breakdown limiting its prospects for repair processes. However, natural $CD4^+CD25^+FoxP3^+$ regulatory T cells were enhanced by prophylactic application of IVIg in an EAE study of Ephrem et al. (2008) suggesting a potential benefit of this therapy in early onset MS.

In other therapeutic trials, two treatments have been combined in order to achieve synergistic effects and/or to reduce adverse side-effects of single agents. For example, combined application of MP and erythropoietin protected neurons and axons of retinal ganglion cells and optic nerve of rats with MOG-induced EAE from morphological and functional impairment, whereas monotherapy caused only isolated neuronal or axonal protection without clinical benefit (Diem et al., 2005). In a MBP-induced active rat EAE model, the anti-inflammatory, anti-demyelinating and neuroprotective effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitory statins could be improved by combination with the selective phosphodiesterase-4 inhibitor rolipram (Paintlia et al., 2008; Paintlia et al., 2009) or the protein kinase A activating substance 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (Paintlia et al., 2006), even when the statin was applied in suboptimal doses. For rolipram alone, beneficial effects in the animal model could previously not be reproduced in the human system (Zhu et al., 2001). In actively induced chronic murine EAE a synergistic therapeutic effect of IFN-β and the immunomodulatory drug laquinimod was observed (Runström et al., 2006). In a patient study, the IFN-β-mediated up-regulation of the anti-inflammatory cytokine IL-10 was enhanced by additive administration of the non-selective phosphodiesterase inhibitor pentoxiphylline (Weber et al., 1998). Pentoxiphylline also reduced side-effects of IFN-β therapy such as myalgia, fever and injection site reactions (Rieckmann et al., 1996). IVIg decreased T cell apoptosis and liver damage, but increased ODC apoptosis in high-dose MBP-treated rats with AT-EAE induced by MBP-specific T cells (Weishaupt et al., 2002). But there are also perilous combination effects, which cannot always be foreseen and thereby prevented in the animal model as illustrated by the hazardous combination of IFN-β with natalizumab (Hartung et al., 2009; Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005; Stüve and Bennett, 2007) or statin (Birnbaum et al., 2008).

While disease-modifying agents act largely through modulation of peripheral immune mechanisms, some of them appear to act additionally or even predominantly locally within the CNS, e.g. at the BBB like IFN-β (Dhib-Jalbut and Marks, 2010) and natalizumab (Rice et al., 2005), on resident auto-reactive T cells and ODC like fingolimod (Miron et al., 2008, 2010; Papadopoulos et al., 2010). When entering the CNS via a locally disrupted BBB at lesion site, IFN-β may also directly act on astrocytes (Boutros et al., 1997) and microglia (Prinz et al., 2008) and even exert direct protective effects on neurons (Plioplys and Massimini, 1995).

3.3. Therapy failures in MS

On the other hand, there are several examples of compounds which were quite effective in curtailing disease activity in the animal model but turned out to lack therapeutic utility or proved to generate inacceptable adverse effect in MS patients. These inconsistencies prompted Sriram and Steiner (2005) to consider EAE a "misleading model of MS". Examples for therapy failures in MS are given in Table 3. Reasons for the discrepant result obtained in the animal and human systems could be manifold. Their nature may be genetic (species differences, peculiarities of inbred animal strains), pathogenetic (individual variability between MS patients) or kinetic (different ontogeny and biorhythms, temporal differences

Table 3
Failure of translation of experimental therapies from the animal model to the clinical practice (selected examples).

Therapy	Results in MS patients	References
Anti-TNF-α mAb infliximab	Increased MRI activity	van Oosten et al. (1996)
Anti-CD3 and anti-CD4 antibodies	No significant clinical effect	Wiendl and Hohlfeld (2002)
Anti-CD28 mAb TGN-1412	Cytokine storm causing multiple organ failure	Hünig (2007)
Altered peptide ligands	Anaphylactic reactions and exacerbation of MS	Bielekova et al. (2000), Kappos et al. (2000)
Oral tolerogens	No significant clinical effect	Faria and Weiner (2006)
Sulfasalazine	Only transient clinical effect	Noseworthy et al. (1998)
Linomide	Cardiopulmonary toxicity	Noseworthy et al. (2000)

The table is reproduced from Mix et al. (2008) with permission of the publisher (Springer).

of immune reactivity and response to therapy). Additionally, in MS the BBB may be insufficiently disrupted as compared to EAE thereby preventing therapeutic molecules to reach their target within the CNS. This seems to be relevant especially when targeting cytokines in MS. For example, the mAb to IL-12 p40 ustekinumab failed to improve relapsing–remitting MS despite promising results in rodent and marmoset EAE (Segal et al., 2008; reviewed in Steinman, 2010). Other promising therapeutic principles revealed already in the animal model limited benefit or adverse effects precluding their use as MS therapeutics. Examples are:

(i) the neuroprotective polypeptide hormone ciliary neurotrophic factor (CNTF), which elicited an acute-phase response in rat liver (Dittrich et al., 1994),
(ii) the anti-adhesion molecule mAb anti-CD54, which revealed no MRI effect in AT-EAE (Morrissey et al., 1996),
(iii) the Na^+-channel blocker phenytoin, which potentially protects demyelinated axons, but resulted in exacerbation of MOG–EAE after withdrawal (Black et al., 2007),
(iv) the phosphodiesterase-4 inhibitor rolipram, while very effective in suppressing EAE, failed to suppress inflammatory activity as gleaned through magnetic resonance imaging in a pilot trial in patients with relapsing–remitting MS (Bielekova et al., 2009),
(v) the immunosuppressive drug cyclosporin A prevented BBB disruption and suppressed the development of EAE, but was classified as unacceptable for treatment of MS based on risk/benefit consideration due to low efficacy and frequent adverse reactions (Goodin et al., 2002; Kappos et al., 1988; Kieseier and Hartung, 2003; McCombe et al., 1999; Paul and Bolton, 1995).

If one therefore considers only the therapeutic trials conducted in EAE and their translation into the clinic, it may well be regarded as a misleading model of MS. However, several aspects of the aetiopathogenesis of MS such as susceptibility genes, immunoregulatory circuits, mechanisms of immune cell activation, migration and elimination as well as of nervous tissue destruction and repair have been successfully studied in EAE rendering it a useful model of MS (Hemmer and Hartung, 2007; Schreiner et al., 2009). EAE will be of continued utility in the future if one capitalizes on the availability of distinct types of EAE, including those induced in transgenic and knockout animals, to explore pathogenic pathways and strategies of intervention in different subtypes or variants of MS.

4. Perspectives

As outlined before, several therapeutic interventions have been successful exclusively in EAE, but not in MS. Other therapeutic agents have shown proven benefit in both EAE and MS. A survey of these agents is given in Table 4. There are also few instances where therapeutic agents for the treatment of MS have been clinically developed without prior evaluation in the animal model. Examples of such drugs including their proposed mechanism of action are listed in Table 5.

Nonetheless, an increasing number of emerging therapies for MS are currently being tested in pre-clinical phases by making use of the EAE model (Cohen and Rieckmann, 2007; Linker et al., 2008c; Weiner, 2009). The most promising experimental therapies rely on gene transfer, stem cell transplantation, oral administration of small molecular weight disease-modifying drugs and intravenous or subcutaneous application of mAb targeting cells or molecules crucial in the pathogenesis of the disease (Aktas et al., 2010; Bielekova and Becker, 2010; Butti et al., 2008; Einstein et al., 2009; Hauser et al., 2008; Hawker et al., 2009; Hemmer and Hartung, 2007; Kieseier and Wiendl, 2007; Pluchino and Martino, 2008; Wynn et al., 2010). Table 6 provides a survey of experimental therapeutic approaches that are currently being investigated, some of which being already approved for phase I-III clinical trials. Table 6 also includes proposed mechanisms of action of the new therapies. Putative targets of established and experimental MS therapies with and without prior testing in EAE are indicated in Fig. 4. Other experimental approaches for MS are based on vaccination, e.g. with pathogenic T cells, TCRs, dendritic cells pulsed with antigen, DNA vaccine encoding MBP, axonal growth inhibitors associated with myelin or pro-inflammatory cytokines. These approaches are extensively reviewed elsewhere (Correale et al., 2008). Recently, a new therapeutic target for a more selective treatment of EAE and MS compared to available therapies has been proposed, i.e. the IL-7-IL-7R pathway that affects pathogenic Th17 cells, but spares regulatory T cells and unrelated immune cells (Liu et al., 2010).

An important field of therapeutic approaches in EAE and MS that will deserve more attention in the future is the enhancement of remyelination. So far experimental trials have involved transplantation of neural stem cells, ODC precursor cells, Schwann cells and olfactory ensheathing cells and application of growth factors such as platelet derived growth factor and epidermal growth factor (Franklin and Ffrench-Constant, 2008). However, these trials are hampered by the fact that the demyelinating

Table 4
Therapeutic agents effective in both MS and EAE.

Agent	Clinically isolated syndrome (CIS)	MS	EAE
Azathioprine		Yudkin et al. (1991)	Błaszczyk et al. (1978), Rosenthale and Gluckman (1968)
Cyclophosphamide		Gauthier and Weiner (2007), Neuhaus et al. (2007), Vollmer et al. (2010)	Mangano et al. (2010)
Fingolimod		Cohen et al. (2010), Kappos et al. (2006b)	Balatoni et al. (2007), Foster et al. (2009), Miron et al. (2008, 2010), Papadopoulos et al. (2010)
Fumarate		Kappos et al. (2008)	Schilling et al. (2006), Kappos et al. (2008)
Glatiramer acetate	Comi et al. (2009)	Comi et al. (2001b), Kieseier and Hartung (2003)	Aharoni et al. (1997, 2008), Racke et al. (2010), Teitelbaum et al. (1971)
IFN-β	Comi et al. (2001a, 2009), Jacobs et al. (2000), Kappos et al. (2006a, 2007)	Kappos and Lindberg (2007), Kieseier and Hartung (2003), Marrie and Cohen (2007)	Dhib-Jalbut and Marks (2010), Ruuls et al. (1996)
Laquinimod		Comi et al. (2008)	Brunmark et al. (2002), Runström et al. (2006), Wegner et al. (2009), Yang et al. (2004)
Methotrexate		Goodkin et al. (1995), Neuhaus et al. (2007), Vollmer et al. (2010)	Lange et al. (2005)
Methylprednisolone		Fox and Kinkel (2007)	Lühder and Reichardt (2009)
Mitoxantrone		Edan et al. (2007), Hartung et al. (2002), Krapf et al. (2005), Neuhaus et al. (2006a,b), Rieckmann et al. (2004), Vollmer et al. (2010)	Ridge et al. (1985), Neuhaus et al. (2006a)
Natalizumab		Polman et al. (2006); Rice et al. (2005)	Rice et al. (2005), Yednock et al. (1992)

Table 5
Experimental therapies for MS evaluated in clinical trials without prior investigation in the animal model (selected examples).

Therapy	Proposed mechanism of action	References
Monoclonal antibodies		Bielekova and Becker (2010), McLaughlin and Wucherpfennig (2008), Linker et al. (2008c)
- Rituximab,ocrelizumab, ofatumumab	Anti-CD20 inhibits B cells.	Hauser et al. (2008), Hawker et al. (2009)
- Daclizumab	Anti-CD25 inhibits lymphocyte activation and expands subpopulation of regulatory T cells.	Rose et al. (2007), Wynn et al. (2010)
- Alemtuzumab	Anti-CD52 depletes lymphocytes.	CAMMS 223 Trial Investigators (2008), Jones and Coles (2008)
Teriflunomide	Dihydro-orotate dehydrogenase inhibitor disrupts the immunologic synapse.	O'Connor et al. (2006), Zeyda et al. (2005)
Temsirolimus	Antifungal antibiotic rapamycin acts immunosuppressive.	Carlson et al. (1993), Keever-Taylor et al. (2007)
Cladribine	2-Chloro-2′-deoxyadenosine alters binding of transcription factors to the gene regulatory AT-rich sequences; accumulated cladribine nucleotides disrupt DNA synthesis and repair and suppress $CD4^+$ and $CD8^+$ T cells.	Foley et al. (2004), Giovannoni et al. (2010), Hartung et al. (2010), Sipe et al. (1996)

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Table 6
Experimental therapies for MS as tested in EAE.

Therapeutic approach	Proposed mechanism of action	References
Gene therapy		Furlan et al. (2003)
- IL-4	Inhibits Th1 cell activation.	Broberg et al. (2004), Butti et al. (2008)
- IFN-β	Inhibits local autoimmune reaction in the CNS.	Makar et al. (2008a)
Stem cell transplantation		Scolding (2006)
- Mesenchymal stem cells	Modulate T cell function, decrease IL-17 via IL-23 secretion.	Pedemonte et al. (2007), Wang et al. (2008)
- Neural stem cells	Down-regulate inflammation, stimulate the endogenous brain repair system.	Aharonowiz et al. (2008), Einstein et al. (2006, 2009), Martino and Pluchino (2007), Pluchino and Martino (2008)
Neurotrophic factors		Mirowska-Guzel (2009)
- BDNF	Reduces inflammation and apoptosis.	Makar et al. (2008b)
- Erythropoietin	Activates the neuroprotective phosphatidylinositol 3-kinase/Akt pathway, down-regulates glial MHC class II.	Agnello et al. (2002), Sättler et al. (2004), Yuan et al. (2008)
Monoclonal antibodies		Buttmann and Rieckmann (2008), Lutterotti and Martin (2008), Rose et al. (2008)
Natalizumab	Anti-CD49d inhibits lymphocyte adhesion.	Rice et al. (2005), Stüve and Bennett (2007)
Anti-cytokines	Small molecular weight drug suppresses pro-inflammatory cytokines.	Karpus et al. (2008)
CRYAB	Stress protein αB-crystallin has an anti-inflammatory effect.	Ousman et al. (2007)
Beta-lactam antibiotic	Ceftriaxone modulates myelin antigen presentation and impairs antigen-specific T cell migration into the CNS.	Melzer et al. (2008)
Steroids	Estradiol and progesterone increase BDNF and myelination.	Garay et al. (2008)
Statins	3-Hydroxy-3-methylglutaryl-coenzymeA-reductase inhibitors prevent geranyl-geranylation of RhoA GTPase and its tethering to the membrane and thereby inhibit T cell activation and infiltration into the CNS.	Aktas et al. (2003), Mix et al. (2006), Stanislaus et al. (1999), Waiczies et al. (2008), Youssef et al. (2002)
Fingolimod (FTY720)	Sphingosine-1-phosphate agonist reduces systemic T and B cell response as well as auto-reactive T cells in the CNS and it promotes remyelination by stimulation of ODC function.	Balatoni et al. (2007), Foster et al. (2009), Kappos et al. (2006b), Miron et al. (2008, 2010), Papadopoulos et al. (2010)
Fumarate (BG-12)	Fumaric acid esters increase the anti-inflammatory cytokine IL-10.	Schilling et al. (2006)
Minocycline	Inhibits matrix metalloproteinases and thereby T cell transmigration.	Brundula et al. (2002)
Gemfibrozile, fenofibrate, ciprofibra	Peroxisome proliferator-activated receptor (PPAR)-α agonists increase the anti-inflammatory cytokine IL-4.	Lovett-Racke et al. (2004)
Laquinimod	Linomide-derivative ABR-215062 changes the cytokine balance towards the anti-inflammatory cytokines IL-4, IL-10 and TGF-β	Brunmark et al. (2002), Comi et al. (2008), Runström et al. (2006), Wegner et al. (2009), Yang et al. (2004)
AICAR	Protein kinase A activating 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside inhibits the pro-inflammatory cytokines IFN-γ and TNF-α and induces the anti-inflammatory cytokines IL-4 and IL-10.	Nath et al. (2005)
CYLA	Calpain inhibitor reduces inflammatory infiltration, demyelination and axonal injury.	Hassen et al. (2008)
3,4-DAA	Derivative of tryptophan metabolite N-(3,4,-Dimethoxycinnamoyl) anthranilic acid inhibits pro-inflammatory cytokines.	Platten et al. (2005)
EGCG	Green tea constituent (−)-epigallocatechin-3-gallate blocks proteasome complex, proliferation and TNF-α production of encephalitogenic T cells and formation of neurotoxic reactive oxygen species.	Aktas et al. (2004)

Table 6 (*Continued*)

Therapeutic approach	Proposed mechanism of action	References
Flavonoids	Luteoline scavenges oxygen radicals, inhibits RhoA GTPase and prevents monocyte infiltration into the CNS.	Hendriks et al. (2004)
Metallothionein I and II	Antioxidant proteins act anti-inflammatory and neuroprotective.	Espejo et al. (2005)
Vitamin D	1,25-Dihydroxyvitamin D3 declines inducible nitric oxide synthase, chemokines and monocyte recruitment into the CNS and stimulates activated $CD4^+$ T cell apoptosis in the CNS.	Pedersen et al. (2007)
K^+-channel blocker	Alkoxypsoralens, kaliotoxin, charybdotoxin, psora-4, bupivacaine, anandamide, spermine and ruthenium red inhibit T cell activation.	Beeton et al. (2001), Meuth et al. (2008), Strauss et al. (2000), Wulff et al. (2009)
Na^+-channel blocker	Phenytoin, flecainide and lamotrigine prevent axonal degeneration.	Bechtold et al. (2004), Bechtold et al. (2006), Lo et al. (2003)
Dopamine receptor antagonists	DRD1 antagonist SCH23390 blocks dopamine receptors on Th17 cells.	Nakano et al. (2008)
Glutamate receptor antagonists	AMPA/kainate antagonists NBQX and MPQX prevent glutamate-mediated demyelination and neuronal death.	Smith et al. (2000)
Histamine receptor antagonists	Histamine-1 receptor antagonist hydroxyzine blocks mast cell degranulation.	Dimitriadou et al. (2000)
Serotonin reuptake inhibitors	Venlafaxine suppresses pro-inflammatory cytokines.	Vollmar et al. (2008)
Bifunctional hybrid molecules		
Bifunctional peptide inhibitor (BPI)	Hybrid peptides made of integrin $CD11a_{237-246}$ and antigenic epitopes $PLP_{139-151}$ or glutamic acid decarboxylase $GAD_{208-217}$ block the immunologic synapse.	Kobayashi et al. (2008)
Fulleren hybrid molecule (ABS-75)	Hybrid molecules made of an antioxidant carboxy-fullerene moiety and NMDA receptor-targeting adamantyl groups inhibit oxidative injury, chemokine expression, $CD11b^+$ cell infiltration, demyelination and axonal loss.	Basso et al. (2008)

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Table 7
Comparison of immunopathological, clinical and therapeutic features of EAE and MS.

	EAE	MS
Genetics	Susceptible and resistant animal strains and colonies, e.g. C57BL/6 vs C57BL/10.S mice and different colonies of Lewis rat	Weak evidence of association (confirmed only for HLA-DRB1*15), risk alleles: IL-2RA, IL-7RA and EV15
Pathology		
- Inflammation	Dominant ($CD4^+$ T cells and macrophages)	Rare (type I/II, $CD4^+$/$CD8^+$ T cells, $CD20^+$ B cells, macrophages)
- Demyelination	Rare (anti-MOG–EAE)	Strong
- Degeneration	Late (murine EAE)	Early (type III/IV)
- Cortical lesions	Rare (MOG–EAE in marmosets)	Rare
Clinical course		
- Acute	Frequent (active EAE)	Rare (Marburg type)
- Primary chronic-progrssive	Rare (MOG–EAE, AT-EAE)	Rare (<10%)
- Relapsing–remitting	Rare ($PLP_{139-151}$–EAE, pertussis toxin-EAE)	Frequent (>90%)
- Immunotherapy		
- Immunosuppression/ immunomodulation	Azathioprine, IFN-β, glatiramer acetate, gene therapy, stem cell transplantation, mitoxantrone, mAb, small molecular weight disease-modifying drugs	Azathioprine, IFN-β, glatiramer acetate, plasma exchange, immunoadsorption, mitoxantrone, mAb, IVIg
- Anti-inflammatory	Methylprednisolone	Methylprednisolone
- Antigen specific	Altered peptide ligands, bifunctional peptide inhibitors, oral and nasal tolerance, DNA vaccines	
- Neuroprotective	CNTF, BDNF, erythropoietin	

lesions are regularly wide-spread and dispersed within the CNS and that they, additionally, lack stimulating factors of ODC precursor cell recruitment and differentiation, or even contain inhibitory factors of remyelination like the neurite outgrowth inhibitor-A (Nogo-A) and its receptor component leucin-rich repeat and Ig domain containing-1 (Lingo-1) (Pernet et al., 2008). Therefore, current efforts to enhance remyelination in EAE and MS rely mainly on established therapies with remyelinating potency such as IVIg, especially polyclonal IgM (Bieber et al., 2000; Trebst and Stangel, 2006; Wright et al., 2009), glatiramer acetate (Aharoni et al., 2008; Arnon and Aharoni, 2009; Racke et al., 2010) and fingolimod (Miron et al., 2008, 2010) or on the application of antagonists of the remyelination inhibitors Nogo-A and Lingo-1 (Bourquin et al., 2008; Mi et al., 2007, 2009; Rudick et al., 2008; Yang et al., 2010).

This review is restricted to the EAE model of MS and a short reference to the toxic cuprizone-mediated model of demyelination. Further information on advantages and disadvantages of EAE and additionally of virus-mediated demyelinating diseases can be derived from the excellent monograph "Experimental models of multiple sclerosis" edited by Lavi and Constantinescu (2005).

In summary, specific questions of MS genetics, pathogenesis and therapy require investigations in different available and forthcoming EAE models. A comparison of the most important immunopathological, clinical and therapeutic features of EAE and MS is given in Table 7. Thereby it becomes obvious that great precaution is advisable when translating the results of experimental therapeutic trials into clinical practice.

Conflict of interest

Eilhard Mix, Hans Meyer-Rienecker, Hans-Peter Hartung and Uwe K. Zettl have no conflict of interest related to this review to declare.

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