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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 γδ⁺ 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.

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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; PDP, 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 paralysis 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 (Mättättä et al., 1998)

to small encephalitogenic peptides (Eylar et al., 1970; Lennon et al., 1970) such as MBP1–37, MBP1–11, MBP1–9, MBP83–99, MOG55–75 and PLP139–151, 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/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 (Kishnamoorthy et al., 2009) and the astrocyte-typical Ca2+-binding protein S100B (Kojima et al., 1997). The neurofascins NF 155 and NF 186 and the adhesion molecule contactin-2/TAG-1 have 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-
atation. 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 expressed juxtaparanodally by both the myelin and axonal membrane forming dimers or molecular zippers (Mo¨rtl et al., 2007; Shimoda and Watanabe, 2009). Whether lipids, glycolipids and phospholipids play also a role as auto-antigens in EAE and MS is still a matter of controversy. In mice lymphocytic choriomeningitis virus protein expression could elicit chronic autoimmune inflammation and demyelination in the CNS (Dziedzic et al., 2010; Siffirin 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 (Siffirin et al., 2010).

Concerning the aetiopathogenesis of MS the role of infections is still a matter of controversy. In mice lymphocytic choriomeningitis virus protein expression could elicit chronic autoimmune inflammation and demyelination in the CNS (Evans et al., 1996). A Chlamydia pneumoniae-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 (Seehusen and Baumga¨rtner, 2010) are suitable models for 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 (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; Siffirin 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 (Siffirin et al., 2010).

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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), Matthey 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), Matthey 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) |
| 510β                      | 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 GM3, sulfatide and galactosylceramide | Increased reactivity of pro-inflammatory cytokine secreted by CD8+ T cells in MS patients | Shamiliev 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 lacto-β-lysophosphatidylserine | Strong antibody reactivity in serum and cerebrospinal fluid of MS patients | Kanter et al. (2006), Quintana et al. (2008b)                             |

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 (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 (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 (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 (Pomeroy et al., 2008).
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 be overcome by approaches with inducible spatially and temporally restricted gene targeting, which has been only recently introduced for studies directed to the CNS (Gavéraux-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 bis(cyclohexane-none oxalhydrazone) (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.

**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.
1.3. Current EAE models

Currently, the most common mode of EAE induction is based on the injection of an encephalitogenic peptide, mostly MOG35–55 or PLP139–151, 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, PLP139–151 induces a relapsing–remitting EAE in SJL mice, whereas MOG35–55 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 alternating 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 epitope. MOG-TCR transgenic T cells that cannot 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 intergenic 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/J 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)-2, IL-7 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; Dabbeek 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 allele (Barcellos et al., 2006; Chao et al., 2008), whereas transgenic mice over-expressing the human HLA-DRB1*1502 allele 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 MOG35–55–EAE of congenic NOR/LJ 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 MOG35–55–EAE mice over-expressing the TCR for MOG35–55 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.
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. Transcriptomic and proteomic analyses are powerful new tools for the elucidation of those genetic screens and high-throughput gene expression studies in animals to lymphatic and nervous tissue (Goertsches and Zettl, 2006; Fathallah-Shaykh, 2005). The same is true for the global gene expression analysis. In any case, due to its obvious limitations transcriptomics should be employed only with a clear transcriptional level, which are consistent with the histological and clinical phenotype. They can serve as a tool for fingerprinting of researchers to identify genes which support maintenance of the mesenchymal stem cells that can ameliorate EAE (Pedeomonte et al., 2004). Moreover, data of Baranzini et al. (2005) derived from the MOG35–55–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 as a source for therapeutic mesenchymal stem cells that can ameliorate EAE (Pedeomonte 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

### Table 2

| Gene Function | References |
|---------------|------------|
| Antigen presentation | Barcellos et al. (2006), Chao et al. (2008), IMSC (2007), Khare et al. (2005) |
| T and B cell activation | IMSC (2007) |
| T cell survival, differentiation and homeostasis, B cell development | Gregory et al. (2007), IMSC (2007) |
| GTpase activation | Dabbeekeh et al. (2007), Hoppenbrouwers et al. (2008) |
| Ligand of CD2, costimulatory molecule for T cells enhancing Foxp3 expression in Treg cells | De Jager et al. (2009a), Hoppenbrouwers et al. (2009) |
| 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) |
| Bacterial molecular pattern recognition and suppressing TNF-α, IL-6 and IL-1β | De Jager et al. (2009b), Sarrias et al. (2007) |
| Activation or repressing of IFN type I transcription | De Jager et al. (2009b), Johnson et al. (2010) |
| Pro-inflammatory and proapoptotic activity | De Jager et al. (2009b) |
| Development of neuronal cells, tumor suppression and anti-inflammation | De Jager et al. (2009b) |
| Growth factor for activated T and NK cells, enhancing the lytic activity of NK/lymphokine-activated killer cells | Rubio et al. (2008) |
| Activation of T cell factor signaling | De Jager et al. (2009b) |
| B cell activation | Johnson et al. (2010) |
| Intracellular signal transduction of type I IFNs | Johnson et al. (2010), Mero et al. (2010) |
| Intercellular adhesion, lymphocyte signaling, cytotoxicity and lymphokine secretion mediated by cytotoxic T cells and NK cells | Haffer et al. (2009) |
| Motor protein transporting mitochondria and synaptic vesicle precursors | Aulchenko et al. (2008) |
| Transport of nonribosome-associated cytoplasmic 5S rRNA to the nucleolus for assembly into ribosomes. | Rubio et al. (2008) |

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 which 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 Pelayé 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 MOG35–55–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 MOG35–55–EAE model led to new conclusions such as
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 histopathological 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 andagger, the axon; Medici et al., 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; Steinman, 2007) and MS (Gold and Lüder, 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 MOG35–55–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 MOG35–55–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
ment approaches, e.g. by associative conditioning (Jones et al., 2009; Hohlfeld et al., 2008; Martin Mdel and Monson, 2007; Weiner, 2009; Ziems en and Ziems en, 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. Anti-myelin antibodies are supposed to be major components of the histopathologic MS pattern II according to Luchinetti 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 γδ T cell subset bearing TCRγδ. 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 γδ 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 MPB 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.](image-url)
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 MStherapeutics, 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; Stuve 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; Lindá, 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 (Paintila et al., 2008; Paintila et al., 2009) or the protein kinase A activating substance 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (Paintila 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; Stuve 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 CDC 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 unacceptable 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 | Hüng (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) |
| Lipomide | Cardiopulmonary toxicity | Noseworthy et al. (2000) |

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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 are 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

| Agent            | Clinically isolated syndrome (CIS) | MS                      |
|------------------|------------------------------------|-------------------------|
| Azathioprine     | Yudkin et al. (1991)               | Blaszczyk et al. (1978), Rosenthal 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) Schilling et al. (2006), Kappos et al. (2008), Aharoni et al. (1997, 2008), Racke et al. (2010), Teitelbaum et al. (1971) |
| Fumarate         | Kappos et al. (2008)               |                         |
| Glatiramer acetate | Comi et al. (2009)                |                         |
| IFN-β            | Comi et al. (2001a, 2009), Jacobs et al. (2000), Kappos et al. (2006a, 2007) | Dhibil-Jalbirt and Marks (2010), Ruuls et al. (1996) |
| Laquinimod       | Comi et al. (2008)                 | Brunnmark et al. (2002), Runström et al. (2006), Wegner et al. (2009), Yang et al. (2004) Langle et al. (2005) |
| Methotrexate     | Goodkin et al. (1995), Neuhaus et al. (2007), Vollmer et al. (2010) |                       |
| Methylprednisolone | Fox and Kinkel (2007)              | Lühder and Reichardt (2009) |
| Mitoxantrone     | Edan et al. (2007), Hartung et al. (2002), Kräpf 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 | | |
| - Rituximab, ocrelizumab, ofatumumab | Anti-CD20 inhibits B cells. | Bielekova and Becker (2010), McLaughlin and Wucherpfennig (2008), Linker et al. (2008c) |
| - Daclizumab | Anti-CD25 inhibits lymphocyte activation and expands subpopulation of regulatory T cells. | Hauser et al. (2008), Hawker et al. (2009) |
| - Alemtuzumab | Anti-CD52 depletes lymphocytes. | Rose et al. (2007), Wynn et al. (2010) |
| 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 | | |
| - IL-4 | Inhibits Th1 cell activation. | Furlan et al. (2003), Broberg et al. (2004), Butti et al. (2008) |
| - IFN-β | Inhibits local autoimmune reaction in the CNS. | Makar et al. (2008a), Solding (2006) |
| Stem cell transplantation | | |
| - Mesenchymal stem cells | Modulates T cell function, decrease IL-17 via IL-23 secretion. | Pedemonte et al. (2007), Wang et al. (2008), Ahsanowiz et al. (2008), Einstein et al. (2006, 2009), Martino and Puchinho (2007), Puchinho and Martino (2008) |
| - Neural stem cells | Down-regulate inflammatory, stimulate the endogenous brain repair system. | NeuroTrophin and Matthias (2008a), NeuroTrophin and Matthias (2008b), Buttmann and Rieckmann (2008), Lutterotti and Martin (2008), Rose et al. (2008) |
| Neurotrophic factors | | |
| - BDNF | Reduces inflammation and apoptosis. | Mirowska-Guzel (2009), Makar et al. (2008b) |
| - Erythropoietin | Activates the neutrophilic phosphatidylinositol 3-kinase/Akt pathway, down-regulates glial MHC class II. | Agnello et al. (2003), Sattler et al. (2004), Yuan et al. (2008) |
| Monoclonal antibodies | Anti-CD40d inhibits lymphocyte adhesion. | Buttmann and Rieckmann (2008), Lutterotti and Martin (2008), Rose et al. (2008) |
| Anti-cytokines | | |
| CRYAB | Small molecular weight drug suppresses pro-inflammatory cytokines. | Karpus et al. (2008), Ousman et al. (2007) |
| Beta-lactam antibiotic | Stress protein eCB-crystallin has an anti-inflammatory effect. | Melzer et al. (2008) |
| Steroids | Estradiol modulates myelin antigen presentation and impairs antigen-specific T cell migration into the CNS. | Garay et al. (2008), Akats et al. (2001), Mix et al. (2006), Stanislaus et al. (1999), Waiczies et al. (2008), Yoshis et al. (2002) |
| 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. | Tamaki et al. (2008), Foster et al. (2009), Balatoni et al. (2007), Kappos et al. (2006b), Papadopoulos et al. (2010), Papadopoulos et al. (2010) |
| 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), Nath et al. (2005), Nath et al. (2005) |
| Fumarate (BG-12) | Fumaric acid esters increase the anti-inflammatory cytokine IL-10. Inhibits matrix metalloproteinases and thereby T cell transmigration. | Schilling et al. (2006), Brunilda et al. (2002), Lovett-Racke et al. (2004) |
| Minocycline | Peroxisome proliferator-activated receptor (PPAR)-α agonists increase the anti-inflammatory cytokine IL-4. | Comi et al. (2008), Runstrom et al. (2006), Wegener et al. (2009), Yang et al. (2004) |
| Gemfibrozil, fenofibrate, ciprofibra, Lovastatin | Linomide derivative ABR-215062 changes the cytokine balance towards the anti-inflammatory cytokines IL-4, IL-10 and TGF-β. | Comi et al. (2008), Brunda et al. (2002), Lovett-Racke et al. (2004) |
| AICAR | Protein kinase A activating 5-aminimidazole-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. | Comi et al. (2008), Runstrom et al. (2006), Wegener et al. (2009), Yang et al. (2004) |
| CYLA | Calpain inhibitor reduces inflammatory infiltration, demyelination and axonal injury. | Hassen et al. (2008) |
| 3,4-DAA | Derivative of tryptophan metabolite N-(3,4-Dimethoxyxycinnamoyl)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 ecephalitogenic T cells and formation of neurotoxic reactive oxygen species. | Akats et al. (2004) |
lesions are regularly wide-spread and dispersed within the CNS and that they, additionally, lack stimulating factors of ODC derived from the excellent monograph “Experimental models of demyelination and neuronal death.”

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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