Biochimica et Biophysica Acta 1812 (2011) 177–183

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Mouse models for multiple sclerosis: Historical facts and future implications

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ARTICLE INFO

Article history:
Received 12 September 2009
Received in revised form 4 June 2010
Accepted 16 June 2010
Available online 25 June 2010

Keywords:
Multiple sclerosis
Experimental autoimmune encephalomyelitis

ABSTRACT

Multiple sclerosis (MS) is an inflammatory and demyelinating condition of the CNS, characterized by perivascular infiltrates composed largely of T lymphocytes and macrophages. Although the precise cause remains unknown, numerous avenues of research support the hypothesis that autoimmune mechanisms play a major role in the development of the disease. Pathologically similar lesions to those seen in MS can be induced in laboratory rodents by immunization with CNS-derived antigens. This form of disease induction, broadly termed experimental autoimmune encephalomyelitis, is frequently the starting point in MS research with respect to studying pathogenesis and creating novel treatments. Many different EAE models are available, each mimicking a particular facet of MS. These models all have common ancestry, and have developed from a single concept of immunization with self-antigen. We will discuss the major changes in immunology research, which have shaped the EAE models we use today, and discuss how current animal models of MS have resulted in successful treatments and more open questions for researchers to address.

1. Introduction

The rodent model for multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE), has been extensively utilized to unravel the mechanisms of autoimmune inflammation. Immunization against myelin antigens will not exactly mimic the mechanisms behind disease onset in humans, but when a putative treatment for multiple sclerosis has been identified, efficacy of this treatment in different EAE models will often be a test of its relevance to the human condition. Indeed, many therapeutics tested in multiple sclerosis patients are in fact based on concepts derived from EAE data. In the case of MS, we are dealing with a pathological state dependent on immune cell trafficking and cytokine production, which means that there are numerous potential targets for treatment during disease development. Firstly, attempts can be made to inhibit the initial development of the pathogenic population. Secondly, the migration of cells into the site of inflammation can be impaired. Finally, the effector molecules produced by this population can be neutralized. In order to identify a therapeutic target playing a role in any of these phases, or to minimize side effects brought on by treatment with a particular medication, the precise molecular mechanisms behind pathogenicity must be uncovered. We will discuss some of the models utilized to discover the mechanisms behind autoimmunity and in treatment development, and their development.

2. From rats to mice

Up until the 1980s, rats were the laboratory animals of choice concerning the study of MS. Their popularity perhaps stemmed from their being one of the first models to be used as laboratory animals. Perhaps it was the case that this model worked well. If compared to mice, rats have the advantage of being large in size, and therefore easier to work with their central nervous system (CNS), with relatively easy methods to isolate and analyze spinal cord and brain. In addition, it is much easier, compared with mice, to perform transplantation-based *in vivo* experiments or intravital microscopy.

Of the different rat strains, the Lewis rats are the most popular in EAE experiments. The disease in Lewis rats is very consistent and relatively straightforward to induce. The lack of dependency on pertussis toxin to achieve disease is also of benefit, as this aspect of disease induction more closely mimics the human situation. Rats immunized with myelin basic protein (MBP) or one of the latter dominant peptides develop disease in around 10 days, if the antigen is emulsified in complete Freund's adjuvant (CFA) [1]. Another way of inducing EAE in rats is by raising myelin-specific T cells by immunization of the rats with a neuroantigen in CFA, followed by expansion and activation of the T cells in culture. Once these T cells are activated, they will induce EAE when transferred to naïve animals [2]. Manifestation of EAE in Lewis rats consists of acute onset and spontaneous recovery, which resembles the relapse of clinical signs seen in MS. However, demyelination in Lewis rats is absent, and this is a hallmark feature of human MS. Furthermore, inflammation in Lewis rats is predominantly localized in the spinal cord, in stark contrast to MS. Thus, the ease of use of the model has somewhat precluded its suitability. Brown Norway and DA rats also show acute inflammation after immunization with MOG-derived peptides, but also

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doi:10.1016/j.bbadis.2010.06.010

present with demyelination in the CNS [3,4]. Taken together, acute EAE in rats is not a complete model for MS, but rather a robust model to dissect the basic mechanisms involved in T cell-mediated neuroinflammation.

For all the reasons mentioned above, rats remain a popular choice as a model for MS. However, over the course of the 1980s, rats were gradually superseded by mice. Mice are smaller and therefore cheaper, allowing for more experiments and repetitions. As a result, many modern reagents were generated for mice and not for rats. The flow cytometry revolution was accompanied by the generation of monoclonal and polyclonal antibodies specific to mouse (and human) cellular surface antigens. In comparison, fewer antibodies for flow cytometry were developed for rat antigens. The next big revolutions in immunology, most notably the discovery of many new cytokines and defining their function, arrived at the time that mice were the more popular laboratory animals. As a result, the focus shifted to design of reagents for mice rather than rats. Collectively, it is today more practical and productive to use mice as EAE models.

3. Gene-targeting as a driving force in EAE studies

Despite numerous practicalities in the usage of mice compared to rats, the major reason for which mice remain the model of choice for many EAE researchers lies in the generation of numerous immune-deficient mice, made possible and almost routine following the pioneering work of Mario Capecchi, Martin J. Evans and Oliver Smithies [5]. In the late 1980s, "gene targeting" was introduced to the field of immunology. This technique allowed for the inactivation of genes and was rapidly seized upon to delete genes involved in lymphocyte activation and cytokine signaling. By inactivating genes, it is possible to efficiently determine if a protein is essential for a specific mechanism. Obviously, this technology has become very popular in many fields of biology far removed from immunology. Many proteins now have defined function, but their exact role in EAE is not always obvious. In such cases, it makes sense to ablate the gene encoding these proteins and induce EAE. In 1995, the group of Avraham Ben-Nun published a paper that would shape the manner in which many researchers investigate EAE [6]. In this report, EAE was induced in mice with the H-2^b allele of MHC II using a peptide of myelin oligodendrocytes glycoprotein (MOG). Their discovery provided a reliable method to induce the disease in C57BL/6 mice that until then were not commonly used in EAE studies. Previously, a MOG-derived peptide, MOG p35-55, had been shown to induce EAE in mice [7], but the importance of the C57BL/6 strain to gene targeting made these results of great importance. This encephalitogenic potential of the MOG peptide p35-55 allowed inducing EAE in gene-targeted mice, without time consuming and laborious backcrosses. Despite the fact that BALB/c mice can also develop EAE when immunized in the correct fashion [8], C57BL/6 mice still represent the model of choice for many researchers given the relative ease of genomic modification and the increasing availability of immune-deficient mice.

When gene targeting was established, most successful embryonic stem (ES) cell lines were of 129 genetic background. In their publication, Mendel et al. demonstrated that EAE could be induced also in these mice when the MOG peptide is utilized. Therefore it was obvious that mice of that genetic background were among the first used in EAE experiments of gene-targeted mice. One of the first knockout mice used were deficient for the cytokine IL-6. IL-6 is a pro-inflammatory cytokine secreted mainly by macrophages, and high levels of it are found in the CNS of MS patients and EAE animals [9]. It was not surprising therefore to find that mice lacking IL-6 were indeed completely resistant to EAE [10–12]. Resistance was associated with the T cells, as it was found that IL-6 deficient T cells are not capable to induce the disease upon passive transfer [10]. Interestingly, it was found that in mice deficient for IL-6, Th1 or Th2 T cells cannot develop, which was postulated to be the reason for the disease resistance [12]. It took a few more years until the discovery of regulatory T cells, after which the group of Kuchroo solved the problem with respect to IL-6 deficiency: they found that rather than a direct role for IL-6 in the generation of encephalitogenic T cells, the reason for the EAE resistance of these mice was the excessive differentiation of regulatory T cells in the absence of IL-6, a potent suppressor of Foxp3 [13]. After depletion of regulatory T cells, IL-6-deficient mice are again susceptible to EAE. Similar results could be obtained in mice with deficiency in the IL-6 signaling pathway [14].

The original paper of the Ben-Nun group indicated that EAE could be induced in H-2^b mice using the MOG_{35-55} peptide [6]. At the time, this was translated also to the usage of 129 mice. However, it was shown later that 129/Sv mice are resistant to EAE induction using the MOG peptide. In fact, 129/Sv mice were only susceptible to MOG-induced EAE when the IFNgR was genetically ablated on this background [15]. However, on a pure 129/Sv background, mice were susceptible to EAE induction using MOG-peptide [16]. Unlike the C57BL/6 strain, it is clear now that there are actually many different 129 'sub-strains', and some differ among each other as much as C57BL/6 mice differ from BALB/c mice [17]. Given this uncertainty surrounding the 129/Sv background, it was therefore clear that many people continued to backcross the gene-targeted mice, for example to C57BL/6. But in addition, new ES cell lines of the C57BL/6 origin were developed, and they allowed the generation of gene-targeted mice that are of pure C57BL/6 origin [18]. Although the methods used for generation of new ES cell lines have progressed considerably in recent years [19], still all commonly used ES cells lines are either of 129, C57BL/6, BALB/c (which are resistant to EAE) or F1 genetic background. For that reason, the vast majority of mice are made with C57BL/6 ES cells, and these can be directly used in EAE experiments.

Although C57BL/6 mice are now the choice of many EAE researchers, disease induction is of a heterogeneous efficiency. From our experience, disease is very much dependent on the Ptx used, and on many unknown factors. Before C57BL/6 mice became so popular in EAE studies, it was much more common to use SJL/J mice. In contrast to C57BL/6 mice, disease induction is much more reliable. Another important difference between SJL/J and C57BL/6 mice is the possibility to induce passive disease. It is possible to isolate T cell lines and clones specific to the encephalitogenic antigen, when using SJL/J or C57BL/6. But these T cell lines and clones are rarely encephalitogenic when isolated from C57BL/6, while this is not the case for SJL/J T cells. The only reliable manner to induce passive EAE in C57BL/6 mice is by using relatively large number of activated and Th1-polarized MOG-specific T cells.

4. Spontaneous EAE models

Unfortunately no natural animal mutant is known which develops spontaneous MS-like symptoms in a similar fashion to the NOD mouse, which develops autoimmune diabetes. However, the establishment of T cell receptor (TCR)-transgenic animals allowed for the analysis of mice with a T cell repertoire heavily skewed towards specific autoantigens. The first TCR transgenic mouse directed against a myelin antigen was the MBP Ac1-10 specific line from Goverman et al. in H-2^u (B10.PL) mice [20]. In contrast to other similar mouse lines [21,22] this line developed an inconsistent spontaneous EAE in non-SPF mouse facilities giving hints to non-defined environmental triggers of disease. In a clean facility the injection of pertussis toxin to transgenic animals sufficed to induce EAE. Interestingly, under these conditions MBP-specific antibodies were found, but their relevance was not further investigated. Juan Lafaille backcrossed his line to the RAG-1 knockout background and found 100% of spontaneous EAE [23]. His Lab also found that transfer of WT CD4 T cells inhibited the spontaneous development of EAE, which was a major milestone in the discovery of CD4 T_{reg} cells [24]. This finding of a higher rate of spontaneous EAE was later reproduced by other groups using other TCR transgenic mouse

lines. One of the first was the humanized model containing a MBP_{84-102} specific TCR isolated from MS patients, a human MS predisposing MHC class II allele and human CD4 [25]. Introducing the RAG2-knockout background increased the spontaneous EAE in this model from 4% to 100%. Another very interesting spontaneous EAE model was the creation of $PLP_{139-151}$ specific TCR transgenic animals [26]. These mice where backcrossed to either B10.S or SJL/J mice which are highly susceptible to EAE. Interestingly two of the founder lines had such a high incidence of spontaneous EAE when backcrossed to SJL/J, that crossing was not possible beyond the fifth generation. This led to the finding that antigen presenting cells of SJL/J are readily activated, in contrast to those from the congenic B10.S mice [27]. A major milestone in EAE research was the creation of a MOG_{35-55}-specific TCR transgenic mice by Bettelli et al. [28]. These mice (termed 2D2) are now among the most common TCR transgenic animals in EAE research. Although these mice develop spontaneous EAE on WT (non-RAG) background only at a low incidence between 4% and 15%, a larger proportion (more than 30%) of these mice develop optical neuritis [28]. The creation of these mice allowed for the finding of a new spontaneous EAE form, namely opticospinal EAE (OSE). When crossed to B cell receptor knockin Ig H^{MOG} mice [29], the offspring develop with 50% incidence a very consistent neuroinflammation confined to the spinal cord and optic nerve, reminiscent of Devic disease in humans [30,31]. Although the lack of aquaporin-specific antibodies clearly hints at a distinct etiology of both diseases, this model might give clues to site specific inflammation found in different MS types. Since in this mouse, B cells as well as T cells recognize the same antigen, this model, although highly artificial due to combined transgenic TCR and BCR, may reveal much about B-T cell cooperation during the induction of autoimmunity. As indicated above, 2D2 mice develop spontaneous EAE at somewhat different incidences, probably depending on the respective animal facility. Since more than 90% of the T cells express the TCR transgenic Vα and Vβ chains, which are specific for MOG_{35-55} and $I\text{-}A^b$, it came as a big surprise that the spontaneous EAE was unaltered on a MOG-deficient background [32]. This was independently identified in two different labs using two distinct MOG knockout strains [33,34]. A mixture of immunological and biochemical approaches led to the finding that 2D2 T cells as well as a big proportion of primary polyclonal MOG_{35-55}-specific T cells (unpublished) do not only recognize MOG_{35-55} but also a peptide of the axonal cytoskeletal intermediary filamentous protein Neurofilament-M (NFM_{18-30}). When both MOG and NFM were knocked out simultaneously in recipient animals, 2D2 T cells were unable to transfer disease [32]. The discovery that a single T cell can possess specificity to multiple autoantigens of the same target organ may have major implications for the understanding of the development of autoimmunity in general.

Most spontaneous EAE models, including the upper ones described using 2D2 animals, develop acute/chronic forms of EAE. Therefore, the establishment of a MOG-specific TCR-transgenic mouse line developing spontaneous relapsing remitting (RR)-EAE was of major importance [35]. In many cases MS develops as a relapsing-remitting form and therefore, mechanisms governing these processes of disease confinement and resurrection are of relevance to MS research. In "RR-mice" nearly all CD4 T cells are specific for MOG_{92-106}, which is the dominant encephalitgenic MOG epitope in the $H\text{-}2^s$ background [7]. Interestingly this mouse not only spontaneously developed a high frequency of spontaneous RR-EAE, but it was also found that B cells from the endogenous repertoire were recruited to produce high amounts of MOG specific antibodies. The early depletion of B cells with anti-CD20 treatment was inhibiting disease onset and sera of TCR transgenic mice where shown to activate complement and to be pro-pathogenic [35]. This model therefore is highly relevant for the study of pattern II MS where complement deposition and T cells are found in lesions [36,37]. It is also an important model especially since depletion of B cells and plasmapheresis is highly efficient in a subgroup of treatment resistant patients [38]. The most TCR transgenic models are based on CD4 T cells recognizing myelin peptides bound to MHC class II alleles. Three different MHC class I-specific CD8 EAE models are published, two of which also develop spontaneous EAE [39–41]. The first is an adaptation of the antigen to the existing OTI ovalbumin specific mouse line, where ovalbumin was expressed in the cytosol of ODCs under the control of the MBP promotor. F1 offspring developed a very drastic form of neuroinflammation at a very early age of 2 weeks [40]. Using this and similar models, direct killing processes in the CNS can be investigated and visualized [42,43]. Although generation of a CD8 model for MS is in demand, the very early disease onset and the artificial autoantigen of this model will not end the hunt for a better MS like CD8 model. A recently published report used human TCR transgenic mice derived from a CD8 cell clone recognizing PLP_{45-53} bound to the human MHC class I allele HLA-A3 [41]. In this model, 4% of double transgenic animals on the HLA-A3 background developed weak spontaneous motor deficits, demonstrating that HLA-A3 is pro-pathogenic whereas coexpression of HLA-A2 was inhibiting disease, either induced or spontaneous, via early thymic selection pressure on TCR transgenic T cells. Interestingly, Mars and colleagues were able to show that naïve CD8 T cells tolerate oligodendrocytes expressing a neo-self antigen, in this case an influenza hemagluttinin (HA) expressed in these cells using a transgenic approach. When effector CD8 T cells bearing the transgenic TCR specific for HA were transferred into these host mice, demyelination and inflammation were observed in the CNS [44]. Thus, despite the accumulation of CD8 T cells in MS lesions [45], these results still point to a peripheral activation of CD8 T cells and oligoclonal expansion of these experienced T cells in the CNS.

There are more spontaneous EAE models published than described here, but common to all is that they are based on TCR transgenic animals. It seems that at least in mice a relatively high number of myelin specific T cells are a pre-requisite for spontaneous EAE development. Although spontaneous EAE models bear the inherent disadvantage of a heterogeneous disease onset time and varying incidences, their development by transgenesis has resulted in many unexpected and interesting discoveries.

5. Development of MS treatments using murine models

Oftentimes it is through failures that the field of MS research has moved forward. It is also the case that therapies that show incredible promise in animal models will not translate to a successful therapy. For example, antibodies directed to deplete T cells showed no significant beneficial effect in the clinic [46]. However, as in the case of the monoclonal antibody TGN-1412 designed to activate Tregs in a CD28-dependent manner, multiple organ failure can be the consequence [47]. It is thus with an air of caution that we should translate our findings in rodent models to the human system. Despite a number of setbacks, we are fortunately able to discuss a number of successful therapies developed in animal models.

It is unusual that the use of IFN-β to treat MS patients has been a highly successful therapy for 15 years, but we still lack the knowledge as to the mechanisms behind the therapeutic benefits of IFN-β treatment. Therefore, understanding the reasons behind this effect can be of central importance to gaining a deeper understanding of at least some the molecular mechanisms involved in MS pathogenesis. Type 1 interferons such as IFN-β are produced by most cell types in response to virus, bacteria or cellular components thereof. They are in essence proinflammatory cytokines that stimulate the immune response on a number of levels.

Type-I IFN signaling has been shown to induce production of cytokines and chemokines, induce maturation of dendritic cells and induce immunoglobulin class-switching in B cells [48]. Differing outcomes have been reported with respect to the efficacy of IFN-β in controlling EAE, and different studies have reported variable efficacy of IFN-β depending on the animal model used and method of EAE induction or IFN-β treatment. While some reports have shown a clear

clinical score amelioration mediated by IFN-β in murine models [49–51], other investigators have reported that IFN-β has no effect on disease progression [52], or even can lead to exacerbation of the disease [53]. Nevertheless, there is no doubt that the therapeutic properties of IFN-β are related to its impact on the activity of T lymphocytes as deduced from the fact that in vitro treatment of encephalitogenic T cells with IFN-β renders them insufficient to induce passive EAE [54,55]. However, important results from Prinz et al. described how antigen-restimulated T lymphocytes from wild type mice induced a significantly stronger clinical disease state in type I IFN receptor (IFNAR)-deficient mice, indicating that IFNAR expression on host-derived cells is of importance during disease induction [56]. Other recent studies have in fact shown that IFN-β treatment reduces the number of Th17 cells in active MS, while not altering the number of Th1 cells in circulation [57].

On the contrary, IFN-α has been shown to be proinflammatory in the CNS, after mice which overexpress IFN-α in the CNS were shown to suffer from inflammation and subsequent neurodegeneration [58]. However, reports have emerged which outline an anti-inflammatory role for IFN-α in disease pathogenesis. Systemic administration of IFN-α resulted in a reduced mortality in response to endotoxic shock in LPS-challenged mice [59]. This finding was transferable to the field of EAE research, where delivery of IFN-α inhibited actively induced EAE [60]. More recently, and with the advent of genetically modified mice discussed previously, both IFN-β and IFN-γ-deficient animals were shown to be hyper-susceptible to EAE pathogenesis [15,61,62]. Mice deficient in Type 1 IFN receptor also develop a more aggressive experimentally induced colitis [63]. Taken together, enough evidence has been collected to describe a profound anti-inflammatory effect of type 1 interferon, but only under certain conditions. The discrepancy between pro- and anti-inflammatory effects of Type I IFN remains, for now, incompletely understood.

The basis of our understanding of the cell types and molecular effectors mediating the pathogenesis of EAE has escalated dramatically. However, it is important to question some basic principles on which current EAE research has been founded. For example, the observation that myelin-specific Th1 cells were sufficient to induce EAE in mice directed the field of MS research toward IFN-γ, the hallmark cytokine of these pathogenic effector cells. It was clearly demonstrated however that both healthy individuals and MS patients harbor myelin-specific CD4+ T cells, but these cells are more likely to have a Th1 phenotype in MS patients [64]. It was therefore surprising that numerous reports illustrate a protective effect of IFN-γ with respect to EAE pathogenesis. Both IFN-γ-deficient mice and mice treated with neutralizing antibodies designed to inhibit IFN-γ signaling were still susceptible, or even hyper susceptible to EAE [65,66]. IFN-γ enhances antigen presentation via MHC upregulation and also positively regulates Th1 differentiation. On the other hand, a pathogenic role for IFN-γ is supported by genetically manipulated mice, which lack suppressor of cytokine signalling-1 (SOCS1), a negative regulator of IFN-γ [67–69]. A complex and lethal disease initiated by the absence of SOCS1 was prevented using neutralizing anti-IFN-γ antibodies, or when the SOCS1 deficiency was crossed to the IFN-γ-deficient background. Despite many efforts to uncover the mechanism behind a protective role for IFN-γ, answers have remained elusive. It was recently shown that IFN-γ signaling downregulates expression of IL-1R on macrophages [70]. Chen Dong and colleagues were able to describe a crucial role for the IL-1β/IL-1R axis in the development of EAE and early generation of Th17 cells. IL-1 receptor expression in T cells, which was shown to be upregulated after IL-6 signaling, was required for the induction of EAE and Th17 cell differentiation *in vivo* [71]. IL-1β was shown to regulate the expression of the transcription factors RORγt and IRF4 during Th17 cell differentiation, placing IL-1β signaling as an early event in Th17 differentiation. Overexpression of either transcription factor resulted in Th17 cytokine expression independently of IL-1β. Thus, IFN-γ may downregulate IL-1R expression on immune cell types and ultimately diminishes their potential to mount an inflammatory response.

Nearly two decades ago, studies of molecules involved in lymphocyte interaction with inflamed epithelium revealed a critical role for the α4 integrin [72]. Neutralizing antibodies directed against the α4-integrin subunit were clearly shown to reduce the severity of EAE, highlighting the importance of T cell migration into the CNS for the progression of disease [73]. Indeed, understanding this mechanism led to the development of Natalizumab, which proved to be beneficial in reducing infiltrates into the cerebrospinal fluid of MS-patients [74]. The development of Nataluzimab as an effective MS treatment constitutes the bona fide example of a hypothesis driven discovery of a drug, found and developed with the help of the EAE model. However, murine models can also be used retrospectively, as is currently the case with glatiramer acetate, the generic term used for Copaxone. After a sustained period of successful therapy using this substance, researchers are still using actively induced EAE to uncover the mechanisms behind the beneficial actions of this treatment [75–78].

6. Th17 cells in EAE and MS

With respect to Th17 cells in EAE, much focus has been placed on unraveling the transcription factors and cytokine requirements for their development [13,79], and more recently, effector maintenance [71,80]. Given the already pre-existing link between MS lesions and IL-17 production [81], the immunological community believed that a major breakthrough in MS treatment was on the horizon after the discovery that IL-17A-expressing T cells were highly efficient in inducing EAE [82]. While the pathogenic role of Th17 cells has been described in a number of disease models (CIA, EAE, EAU) [83–85], the molecular explanation behind the pathogenicity of Th17 cells is now undoubtedly more complex than this single hallmark cytokine. For example, adoptively transferred Th17 cells failed to induce EAE in C57BL/6 mice [86]. IL-17A-deficient or anti-IL-17A-treated mice are indeed able to develop EAE, though the kinetic and severity of disease is reduced, albeit to varying degrees [87–89]. When one contrasts this milder phenotype with the absolute and reproducible resistance of IL-23p19-deficient or IL-6R deficient mice [14,84], it is clear that IL-23 and IL-6 signaling on T cells results in more than just Th17 development. Indeed, TGF-β and IL-6-polarized Th17 cells per se are not able to induce EAE, even if they are myelin-specific [90]. In contrast IL-23-driven myelin-specific Th17 cells were able to induce EAE [91]. However, the results from a clinical trial using anti-p40 to treat MS patients was unsuccessful, showing that IL-23 in humans may indeed not be the major player in the human condition, and as such highlight possible differences in the molecular requirements for EAE and MS pathogenesis. The clinical trial was, however, conducted on patients with wide ranging MS pathogenesis, and in part after years of suffering with MS. As IL-23 has been shown to be essential in induction of EAE, it was conversely shown to be dispensable for maintenance of disease [92]. Thus, IL-12/23 p40 treatment may function better when administered much earlier in the disease development. IL-17-producing CD4+ and CD8+ T-cells are nonetheless detectable in active and chronic MS, and consist of both CD4 and CD8 T-cells [93]. Thus, elucidating a role for Th17 cells in MS is indeed a worthwhile endeavor, but accumulating evidence from both EAE and clinical trials suggests that the causes of MS are more complex. One must not rule out the current theory that Th17 cells are highly flexible in their cytokine repertoire [94], and although IL-17A expression is indeed linked to Th17 cells, the Th17' phenotype may only represent a stage in the life of an effector cell, and subsequently expressed cytokines are the true pathogenic molecules.

7. Concluding remarks

All current evidence identifies MS as a complex disorder, and as such is safe to conclude at this point that no single animal model of

neuroinflammation will successfully encompass all the factors present in the human condition. MS and EAE are in essence different disease states, and much evidence suggests that the EAE models do not accurately reflect the pathology of a progressive condition, which is the nature of MS. The numerous models of EAE are at best dissimilar in their pathology and immunology, which hampers our certainty of which EAE model will be more suitable. The mice used in EAE experiments are generally inbred, so genetic differences are essentially excluded from analyses and do not reflect what one might encounter in the human population.

On a more positive note however, diversity within the field of EAE has its advantages. Each model may accurately mimic one particular facet of MS. Gene targeting advances in mice allow us to pinpoint molecules of interest with incredible precision, and as such can greatly accelerate the process of identifying proinflammatory mediators and mechanisms behind the inflammation observed in EAE models. Although the commonly used EAE model was criticized for its limitation in the development of MS treatments [95], it has also brought great success in the form of Copaxone and Natalizumab. Another major advantage of EAE models is speed. New results generated in EAE provide rapid indications of whether a particular treatment regimen might be of use when transferred to the human system. Taken together, we must conclude that despite numerous drawbacks, EAE has been an extremely valuable model in investigating the pathogenesis and developing new medications to help those suffering from multiple sclerosis.

Acknowledgments

This work was supported by the DFG grants WA 1600/3-1 and SFB/TR 52 to A.W.

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