European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Animal models of Multiple Sclerosis

Claudio Procaccini [a], Veronica De Rosa [a,b], Valentina Pucino [c], Luigi Formisano [d], Giuseppe Matarese [e,f,*]

[a] Laboratorio di Immunologia, Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR) c/o Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università di Napoli "Federico II", 80131 Napoli, Italy
[b] Unità di NeuroImmunologia, IRCCS Fondazione Santa Lucia, 00143 Roma, Italy
[c] Dipartimento di Scienze Mediche Traslazionali, Università di Napoli Federico II, 80131 Napoli, Italy
[d] Divisione di Farmacologia, Dipartimento di Scienze e Tecnologie, Università degli Studi del Sannio, 82100 Benevento, Italy
[e] Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Baronissi Campus, 84081 Baronissi, Salerno, Italy
[f] IRCCS Multimedica, 20138 Milano, Italy

ARTICLE INFO

Article history:
Received 23 January 2015
Received in revised form
30 January 2015
Accepted 12 March 2015

Keywords:
Multiple Sclerosis
EAE
Immune system

ABSTRACT

Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) which involves a complex interaction between immune system and neural cells. Animal modeling has been critical for addressing MS pathogenesis. The three most characterized animal models of MS are (1) the experimental autoimmune/allergic encephalomyelitis (EAE); (2) the virally-induced chronic demyelinating disease, known as Theiler's murine encephalomyelitis virus (TMEV) infection and (3) the toxin-induced demyelination. All these models, in a complementary way, have allowed to reach a good knowledge of the pathogenesis of MS. Specifically, EAE is the model which better reflects the autoimmune pathogenesis of MS and is extremely useful to study potential experimental treatments. Furthermore, both TMEV and toxin-induced demyelination models are suitable for characterizing the role of the axonal injury/repair and the remyelination process in MS. In conclusion, animal models, despite their limitations, remain the most useful instrument for implementing the study of MS.

© 2015 Elsevier B.V. All rights reserved.

UNCORRECTED PROOF

1. Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS) (Hafler et al., 2005). It represents the leading cause of non-traumatic disability among young adults and has a great socio-economic impact in developed countries. MS is a very heterogeneous disease, indeed its clinical signs and symptoms are very variable and depend on the parts of the affected CNS (brain and spinal cord), including motor, sensory, autonomic and cognitive disabilities (Noseworthy et al., 2000). It can run at least three clinical courses: the relapsing–remitting (RR), which is the most frequent (85%) and it is characterized by exacerbations and subsequent periods of clinical stability; secondary progressive (SP) and the primary-progressive (PP) subtype (Noseworthy et al., 2000). CNS tissue from Multiple Sclerosis patients shows discrete lesions with inflammatory infiltrates, demyelination, astrogliosis and early axonal damage. MS is widely considered an autoimmune demyelinating disease, where an autoimmune reaction by myelin-specific $CD4^+$ T helper 1 (Th1) and Th17 cells, which initiate the neuropathology, has been described (Hafler et al., 2005; Sospedra and Martin, 2005). A specific cause for the pathogenesis of MS has not been identified so far, although several genetic and environmental risk factors have been suggested to play a central role. In this context, animal models of MS had allowed to explore mechanisms of disease initiation and progression and test several novel therapeutical approaches for the disease.

2. Positive and negative aspects of MS animal models

Since MS is a complex disease, there is no a single animal model that can capture the entire spectrum of heterogeneity of human MS and its variety in clinical and radiological presentation. However, over the last few years, animal models have been used to study the pathogenic mechanisms of MS. The main positive aspect is that they can surely serve as a testing tool to study disease development and for novel therapeutic approaches. In addition, they are a relatively convenient source of tissue from the CNS, which is the main target of MS, in contrast to human tissues, biopsies, or autopsy samples which are rarely performed. Several researchers have recently raised

* Corresponding author at: Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Baronissi Campus, 84081 Baronissi, Salerno, Italy.
Tel.: +39 081 7464580; fax: +39 081 7463252.
E-mail address: gmatarese@unisa.it (G. Matarese).

http://dx.doi.org/10.1016/j.ejphar.2015.03.042
0014-2999/© 2015 Elsevier B.V. All rights reserved.

the question whether these animal models could really represent a good model for MS since they do not perfectly reflect all the aspects of the human disease. In particular, disease initiation is usually highly artificial in the animal models (induced by active immunization with an auto-antigen). Also the time-frame of the clinical symptoms onset is different between humans and mice. In humans, physiological processes underlying the disease are undetected for years before the onset of clinical manifestations, while symptoms in the animal models can be detected within weeks or even days after induction of the disease. Moreover the treatment in these therapy studies started very early in the course of the induced autoimmune disease, whereas any therapy for humans is administered in a late phase of the disease. More importantly, most of the experimental studies use inbred strains mice with genetic homogeneity and often these mice may have accumulated genetic irregularities that are very difficult to find in human population. Although it has become clear that rodent and human immune systems have profound differences (as they are evolutionarily distant), they share some essential principles and, in this context, the availability of three major animal models of MS allowed the understanding of relevant features of the human MS. The most commonly studied animal models of MS are (1) the experimental autoimmune/allergic encephalomyelitis (EAE); (2) viral induced models, mainly Theiler's murine encephalomyelitis virus (TMEV) infection and consequential chronic demyelination and (3) toxin-induced models of demyelination, such as the cuprizone and the lyso-phosphatidylcholine (lysolecithin) models.

3. Experimental autoimmune encephalomyelitis (EAE)

MS is a chronic, immune-mediated, inflammatory disorder of the CNS (Frohman et al., 2006). The most-studied animal model of MS is the experimental autoimmune encephalomyelitis (EAE), in which autoimmunity to CNS components is induced in susceptible mice through immunization with self-antigens derived from basic myelin protein. Rivers et al. (1933) firstly described, in monkeys immunized with rabbit brain extracts, paralysis associated to perivascular infiltrates and demyelination in the brain and spinal cord, as acute disseminated encephalomyelitis, later called experimental autoimmune encephalomyelitis (EAE). Freund's adjuvant (CFA) (Freund and McDermott, 1942) and pertussis toxin (PT) (Munoz et al., 1984), were later added to potentiate the humoral immune response and to induce oscillatory symptoms typical of the relapsing–remitting disease (Kabat et al., 1947), similar to that found in MS patients. Experiments were also performed in other animal species such as guinea pigs (Freund et al., 1947), monkeys (Kabat et al., 1947; Morgan, 1947); however mice (Olitzky and Yager, 1949) and rats (Lipton and Freund, 1952) resulted the best model to evaluate acute monophasic, relapsing–remitting and chronic progressive EAE through immunogenetic, histopathological and therapeutic studies. EAE in mice is characterized by an ascending paralysis beginning at the tail (Batoulis et al., 2011), followed by limb and forelimb paralysis, assessed by using a 5-points scale (McRae et al., 1992; Rangachari et al., 2012; Berard et al., 2010). EAE may be induced in mice with different genetic backgrounds, such as SJL/J, C57BL/6 and NOD, through either active immunization with protein or peptide, or by passive transfer of encephalitogenic T cells. In all cases, the relevant immunogen is derived from self-CNS proteins such as myelin basic protein (MBP), proteolipid protein (PLP) or myelin oligodendrocyte glycoprotein (MOG). Immunization of SJL/J mice with the immunodominant epitope of PLP ($PLP_{139–151}$) induces a relapsing–remitting (RR) disease course (Tuohy et al., 1989), while disease induced by the immunodominant $MOG_{35–55}$ peptide in C57BL6/J mice is of chronic nature (Tompkins et al., 2002).

More recently a variety of additional antigens have been supposed to be involved in autoimmune reaction in MS and EAE. Some of them are myelin constituents, such as neurofascin NF 155 (Mathey et al., 2007), others are expressed on myelin and axons, such as contactin-2/transient axonal glycoprotein-1 (TAG-1) (Derfuss et al., 2009) and some other are entirely non-myelin antigens, such as the neuronal membrane protein neurofascin NF 186 (Mathey et al., 2007), the neuronal cytoskeletal protein

Table 1
Characteristics of the different mouse models of multiple sclerosis.

Model of MS	Mechanism	Application	Involved cells	Translational value	Main references
Relapsing–remitting EAE in SJL/J mice	Immunization of SJL/J mice with $PLP_{139–151}$	Study of neuroinflmmation and immune system activation	CD8, CD4, Th17, monocytes, macrophages, B cells, Treg cells	Relapsing–remitting MS, study of the relapse rate, testing therapeutical agents	Zamvil et al., 1985; McRae et al., 1995; Whitham et al., 1991; Miyagawa et al., 2010; Adlard et al., 1999
Chronic EAE in C57BL/6J mice	Immunization of C57BL/6J mice with $MOG_{35–55}$	Study of neuroinflmmation and immune system activation	CD8, CD4, Th17, monocytes, macrophages, B cells, Treg cells	Primary progressive MS, secondary progressive MS, testing therapeutical agents	Mendel et al., 1995; Berard et al., 2010; Hjelmstrom et al., 1998; Bullard et al., 2007; Koh et al., 1992; Baron et al., 1993
EAE in transgenic mice	T cell clone (2D2) expressing Vα and Vβ chains reacting specifically to $MOG_{35–55}$, or B cell heavy chain knock-in mouse strain (IgH MOG)	Study of neuroinflmmation and immune system activation	CD8, CD4, Th17, monocytes, macrophages, B cells, Treg cells	*In vitro* study of immune cell activation and function	Bettelli et al., 2003; Litzenburger et al., 1998; Jäger et al., 2009; Encinas et al., 1999; Anderson et al., 2012
Theiler's murine encephalomyelitis virus (TMEV)	Infection with picornavirus, such as Theiler's murine encephalomyelitis virus (TMEV)	Study of axonal damage and inflammatory-induced demyelination	Macrophage/microglia, oligodendrocyte, astrocytes and CD4, CD8	Primary progressive MS, study of brain, brainstem and spinal cord lesions, study of new therapeutic approaches targeting adhesion molecules, axonal degeneration	Tsunoda and Fujinami, 2010; Libbey and Fujinami, 2003; Owens, 2006; Tsunoda et al., 1996; Tsunoda et al., 2003
Cuprizone-induced MS	Feeding C57BL/6 mice with 0.2% cuprizone for 6 weeks	Study of the de- and re-myelination processes	Oligodendrocytes, astrocytes, microglia	Therapeutical trials designed to repress demyelination or accelerate remyelination	Matsushima and Morell, 2001; Blakemore and Franklin, 2008; Lucchinetti et al., 2000
Lysolecithin-induced MS	Lysolecithin injection in SJL/J mice	Study of the de- and re-myelination processes	Oligodendrocytes, astrocytes, microglia	Therapeutical trials designed to repress demyelination or accelerate remyelination	Jeffery and Blakemore, 1995; Shields et al., 1999; Bieber et al., 2003

UNCORRECTED PROOF

Please cite this article as: Procaccini, C., et al., Animal models of Multiple Sclerosis. Eur J Pharmacol (2015), http://dx.doi.org/10.1016/j.ejphar.2015.03.042

Download English Version:

https://daneshyari.com/en/article/5827300

Download Persian Version:

https://daneshyari.com/article/5827300

Daneshyari.com