Animal Models of Multiple Sclerosis: Imperfect but Imperative

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Editorial

Multiple sclerosis (MS) is a complex multifaceted disease involving autoimmune inflammation, demyelination and degeneration processes. The disease is heterogeneous in its clinical manifestation and progression, as well as in its pathological mechanisms [1]. Animal models have been indispensable for MS research. There is however, an ongoing controversy in regard to their true relevance to the human disease.

The most intensively studied MS model, experimental autoimmune encephalomyelitis (EAE), discovered as a rare complication of rabies vaccinations, has been in use for over 80 years [2]. Immunizing rodents or nonhuman primates by self-myelin antigens/epitopes induces an autoimmune response in the CNS, which is typically manifested by ascending tail to limb paralysis. EAE is actually a group of models with different disease courses, depending on the genetic background and the antigen used for immunization [3,4]. Importantly, different pathological patterns are involved in different EAE models, recapitulating the various repertoires of MS. For example, the relapsing-remitting model induced by the myelin proteolipid protein (PLP) peptide in SJL/J mice is characterized by widespread myelin damage, whereas in the chronic model induced by the myelin oligodendrocyte glycoprotein (MOG) peptide in C57BL/6 mice, axonal and neuronal damage are more prevalent [5]. In all these animal models, as well as in MS, the pathological processes occur under an inflammatory background.

The parallels that can be drawn between the EAE models and the MS subtypes facilitated these models’ usage for investigating MS pathophysiology and therapy. However, as time went on, the limitations of the “classical” EAE models became evident. It has been demonstrated that the unique pattern of demyelination characteristic of MS is not accurately portrayed in the EAE models. For example, most opinions claim that the lesion distribution in the widely used MOG-induced EAE in C57BL/6 mice is confined to the spinal cord and the optic nerve, which is more comparable to neuromyelitis optica (NMO) than to MS [3]. However, widespread damage in various brain regions (such as the corpus callosum, striatum, thalamus cerebellum and the cortex) have been demonstrated in this model by immunohistochemistry and magnetic resonance imaging (MRI) [5,6]. An additional criticism is that the classic EAE models lack a B-cell component. Yet, several EAE models, such as those induced by the MOG protein in DA rats and marmosets or by human MOG protein in C57BL/6 mice, were shown to be dependent on B-cells. [4].

A major difference between MS and EAE is that whereas MS occurs spontaneously, the classic EAE models require external immunization, mostly with an adjuvant enriched with bacterial components, which heavily boosts the immune system. A breakthrough in this respect was the development of transgenic mouse strains that manifest spontaneous EAE. In particular, the MOG 35-55 specific TCR-transgenic strain on C57BL/6 background (2D2) and its combined models are now widely used [7]. Still, the involvement of a single transgenic T-cell line in these models is somewhat artificial and does not reflect the complex interactions occurring in the human disease.

Another category of animal models used to investigate the principal features of de- and re-myelination in the CNS is those induced by toxic agents, like the copper chelator cuprizone, that causes demyelination in the relative absence of inflammation [8]. However, due to the lack of an autoimmune inflammatory component, it poorly resembles MS. An additional system used to study myelination is postnatal myelogenesis, as some features of developmental myelination reappear during remyelination [9].

Viral models, such as the Theiler’s murine encephalomyelitis virus (TMEV), are used in view of the suspected role of viruses in MS pathogenesis. Intra cerebral inoculation of TMEV results in an early subtle disease phase. Therapeut, susceptible mouse strains develop brain and spinal cord inflammations, demyelination and axonal damage, with a clinical course that resemble chronic progressive MS [10].

Certainly, the versatile animal models, in particular those of the EAE spectrum, have been highly valuable tools for studying the pathological mechanisms involved in MS, as well for developing therapies and elucidating their mechanisms of action. Yet, in view of the imperfect correlation and the number of therapies found to be successful in EAE suppression but of limited efficacy in MS, the translational relevance of animal models to MS is constantly being debated [11]. It is clear that MS is too complex to be mirrored by a single model. However, combinations of several models and their perceptive interpretations can give a truer prospective of this disease. In this context, the significance of systematic research in actual MS patients using advanced imaging technologies, CNS biopsies and postmortem samples is emphasized.

References


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Received October 07, 2015; Accepted October 12, 2015; Published October 19, 2015


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