Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Experimental models of demyelination and remyelination

L. Torre-Fuentes*, L. Moreno-Jiménez, V. Pytel, J.A. Matías-Guiu, U. Gómez-Pinedo, J. Matías-Guiu

Servicio de Neurología, Instituto de Neurociencias, IdISSC, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Madrid, Spain

Abstract

Introduction: Experimental animal models constitute a useful tool to deepen our knowledge of central nervous system disorders. In the case of multiple sclerosis, however, there is no such specific model able to provide an overview of the disease; multiple models covering the different pathophysiological features of the disease are therefore necessary.

Development: We reviewed the different in vitro and in vivo experimental models used in multiple sclerosis research. Concerning in vitro models, we analysed cell cultures and slice models. As for in vivo models, we examined such models of autoimmunity and inflammation as experimental allergic encephalitis in different animals and virus-induced demyelinating diseases. Furthermore, we analysed models of demyelination and remyelination, including chemical lesions caused by cuprizone, lysolecithin, and ethidium bromide; zebrafish; and transgenic models.

Conclusions: Experimental models provide a deeper understanding of the different pathogenic mechanisms involved in multiple sclerosis. Choosing one model or another depends on the specific aims of the study.

© 2017 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PALABRAS CLAVE

Modelos experimentales; Desmielinización; Remielinización; Esclerosis múltiple;

Modelos experimentales de desmielinización-remielinización

Resumen

Introducción: El uso de modelos experimentales en animales permite aumentar el conocimiento sobre la patología del sistema nervioso central. Sin embargo, en la esclerosis múltiple, no existe un modelo que permita una visión general de la enfermedad, de forma que es necesario utilizar una variedad de modelos que abarquen los distintos cambios que se producen.
Introduction

Experimental models are essential to advancing our understanding of disease and in the design of specific and effective treatments. The development of experimental models of multiple sclerosis (MS) is particularly challenging given that the condition only affects humans and that demyelinating diseases in animals are considerably different from human central nervous system (CNS) diseases. The search for animal models of demyelination has led to the development of both in vitro and in vivo models; the latter include transgenic mice as well as chemically-induced, viral, and autoimmune models. As no such model is comparable to MS, multiple models are needed to cover the different pathophysiological features of the disease.

While MS is an inflammatory disease, it is remyelination failure, incomplete remyelination, and neurodegeneration that lead to disease progression and disability. This is relevant to MS treatment: current treatments only control immune mechanisms and are therefore effective in the early stages of the disease, but have no effect on remyelination and consequently on sequelae. Remyelination is therefore the main focus of new treatment options for MS. This study reviews the currently available experimental models providing information on this stage of the disease and enabling testing of different drugs.

Development

In vitro models

In vitro models of MS consist of cultures of immortalised cell lines or isolated mammalian brain cells, allowing the study of cell-cell interactions. These cell lines may be transformed genetically; they are stable and may be subjected to a wide range of experimental diseases. Studies of CNS cell cultures use microglial cells (mesoderm), neurons, astrocytes, and oligodendrocytes, and also their precursor cells (ectoderm). Studies of microglial cell cultures enable us to extrapolate the role of these cells to CNS immune response in MS, enabling the analysis of microglial response to certain signals, such as biochemical signals, and the potential mechanisms of activation of these cells. Ectodermal-lineage cell cultures allow us to study the cascade of events triggered by demyelination, astrocytic metabolic support in demyelinating lesions, activation and signalling pathways involved in oligodendrocyte replacement, and remyelination of demyelinated axons. Cultures of oligodendrocyte precursor cells or undifferentiated neural stem cells are of particular interest since they allow us to study differentiation and the effect of inflammatory factors, test new chemical compounds aimed at promoting oligodendrocyte proliferation, and develop strategies that may promote remyelination. Our research group has used these cells to introduce mutations associated with Alexander disease and to study myelination mechanisms in the condition. Primary astrocyte cultures are also useful since these cells are involved in the local environment, which is essential in remyelination. Astrocytes express growth factors, such as platelet-derived growth factors and insulin-like growth factor 1, which have been found to promote remyelination. The main disadvantage of in vitro models is that the response of individual cell types may not be extrapolated to tissues. Slice cultures are in vitro models that enable the study of cell-cell interactions and provide a more reliable picture of in vivo conditions. They also allow us to visualise the interaction between the immune system and CNS damage and repair mechanisms, and enable researchers to regulate alterations in oligodendrocyte maturation and remyelination failure due to chronic CNS astrogliosis. Slice cultures have some limitations, particularly the slicing procedure: slices must be 200-500 μm thick, obtained from young or even neonatal animals, and manipulated under special conditions with carbogen gas.
| Model | Species | Agent | Spontaneous remyelination | Advantages | Disadvantages |
|-------|---------|-------|--------------------------|------------|--------------|
| EAE   | Rat     | MOG   | No                       | Relapsing-remitting disease similar to MS | Not useful for studying remyelination |
|       | Mouse   | MBP   |                          |            |              |
|       | Guinea pig | PLP |                          |            |              |
|       | Zebrafish |     |                          |            |              |
|       | Rhesus monkey |  |                          |            |              |
|       | Marmoset |  |                          |            |              |
| TMEV  | Mouse   | Theiler’s murine encephalomyelitis virus | No | Useful for testing treatment strategies specific to the viral model of MS | Difficult to determine to what extent disease is caused by virus activity or by inflammatory response |
| SFV   | Mouse   | Semliki Forest virus | Yes | Suitable for studying virus-induced demyelination/remyelination Mice do not die of neurological disease | Depends on the animal’s immune system |
| JME   | Japanese macaque | Simian herpesvirus | Limited | Spontaneous | No experimental model available |
|       | Mouse   | Mouse hepatitis virus | Yes | Useful for replicating MS pathogenesis Superior to the EAE model for studying progressive disability | It is unclear how the virus infects and spreads through the animal’s CNS |
| MHV   | Mouse   | Lysolecithin | Yes | Localised lesion | Extremely complex technique |
| Lysolecithin | Rat | Lysolecithin | Yes | Enables the precise timing of demyelination and remyelination to be studied Non-inflammatory Specific to oligodendrocytes Localised lesion | Unsuitable for studying the functional characteristics of some strains Complex technique |
| Cuprizone | Rat | Cuprizone | Yes | | |
| Ethidium bromide | Rat | Ethidium bromide | Yes | | |

CNS: central nervous system; EAE: experimental allergic encephalitis; JME: Japanese macaque encephalomyelitis; MBP: myelin basic protein; MHV: mouse hepatitis virus; MOG: myelin oligodendrocyte glycoprotein; MS: multiple sclerosis; PLP: proteolipid protein; SFV: Semliki Forest virus; TMEV: Theiler’s murine encephalomyelitis virus.
Experimental models of demyelination and remyelination

**Figure 1** Induced inflammation and demyelination in in vivo models. (A) Induction in autoimmune and/or inflammatory models. An immunostimulator is administered intramuscularly or subcutaneously. Induced inflammation is associated with increased levels of proinflammatory cytokines, T cells, and activated microglia, leading to the formation of reactive oxygen species (ROS), oligodendrocyte and myelin damage, and reactive gliosis and vessel wall alterations, resulting in oedema. This stage is followed by regeneration, where the number of activated cells (astrocytes and microglia) decreases and oligodendrocyte precursor cells migrate mainly from the corpus callosum (CC) or subventricular zone (SVZ) to replace damaged cells and promote remyelination. (B) Induction in demyelination models. Demyelination is induced with chemicals or toxic agents, which are administered orally (diet), locally (intracerebral), intramuscularly, or subcutaneously. After entering the bloodstream, the chemical or toxic agent enters into contact with axons, causing myelin degeneration; this microenvironment induces microglial activation, ROS formation, inflammatory cytokine release, and reactive gliosis. This ultimately leads to the loss of myelin sheaths and myelin-producing cells (oligodendrocytes). This stage is followed by regeneration, where the number of activated cells (astrocytes and microglia) decreases and oligodendrocyte precursor cells migrate mainly from the CC or SVZ to replace damaged cells and promote remyelination.

**In vivo models**

In vivo experimental models of MS may be classified into 3 categories: (1) autoimmune and/or inflammatory models (Fig. 1A), such as models of experimental allergic encephalitis (EAE) and viral models; (2) models of demyelination/remyelination (Fig. 1B), including models of chemical lesions induced with cuprizone, lyssolecithin, and ethidium bromide, and the zebrafish model; and (3)
transgenic models, which aim to more accurately replicate the key pathological features of the disease (Table 1).14

Autoimmune and inflammatory models

Experimental allergic encephalitis

Experimental allergic encephalitis shares some characteristics with MS: inflammation, demyelination, axonal loss, and glossis. The main difference between the 2 entities is that EAE is experimentally induced, whereas MS must be induced by an immune response. Different protocols have been developed for inducing EAE; the most widely used employ an autoantigen to induce reactive T cell activation (active EAE) or transfer autoreactive T cells to naive animals (passive EAE).6,26 Active induction of EAE requires an adjuvant (most frequently Freund’s Complete Adjuvant), which slowly releases the zoosphenol from the inoculum2 and contains a mycobacterium (most commonly Bordetella pertussis). The bacterium causes clonal expansion of autoreactive T cells, triggering the manifestations typical of MS by promoting harmful immune responses.22 While EAE has been used to study neuroinflammatory and immune response mechanisms, it is also useful for the study of demyelination and remyelination.19 As in MS, age, sex, and environmental factors have a major impact on EAE susceptibility, severity, and progression.15 This model has been tested in several species in search for the species most accurately simulating human MS. It has been tested in primates, such as rhesus monkeys, which displayed disease resembling those seen in autoimmune diseases of patients with MS26; (2) with recombinant human myelin oligodendrocyte glycoprotein (MOG), which causes smaller but longer-lasting demyelinating lesions26,27; and (3) with a subclinical dose of recombinant rat MOG followed by an injection of TNFα and interferon.7,28 Although primate EAE models bear a greater similarity to human MS than rodent models, the use of primates in research has ethical and economic limitations.27

The rodent immune system is considerably different to that of humans but does enable us to assess the chronic, progressive nature of the disease through immunogenetic, histopathological, and treatment studies. In mice, EAE is induced by an immune response triggered by injection of such myelin antigens as myelin proteolipid protein (PLP), MOG,29 and myelin basic protein (MBP); the latter 2 activate microglia and induce perivascular infiltration of T and B cells and even myelin damage, which usually coincides with relapses.30 Mouse models of neuromyelitis optica have also been developed.31,32 The rat model of EAE consists of inflammatory infiltration of mononuclear cells of the spinal cord, cerebellum, and medulla oblongata.13 EAE has also been induced in guinea pigs (Hartley and strain 13). Strain 13 guinea pigs are regarded as one of the animal models best replicating MS since the animals experience chronic relapses.34 EAE has also been induced in zebrafish models.25

Viral models of demyelinating diseases

CNS demyelination has also been induced with viruses. Theiler’s murine encephalomyelitis virus is a murine virus capable of inducing a neurological disease characterised by demyelination due to neuronal infection and mainly manifesting as subclinical encephalitis.36,37 The acute stage is followed by a chronic, progressive stage characterised by spinal cord demyelination and remyelination, resulting in damage to macrophages, microglia, oligodendrocytes, and astrocytes.2,37–39 Spinal cord lesions are characterised by chronic inflammation, confluent demyelinating plaques from the first episode, axonal damage of varying severity, and remyelination. Active demyelination occurs at sites of activated microglia and macrophage infiltration; these lesions therefore present the typical features of MS lesions.2

The avirulent A7 strain of Semliki Forest virus is a neuroinvasive virus that induces CNS myelin damage when injected into susceptible mice. This strain induces viraemia lasting 3–4 days, after which the virus is cleared from the blood. In subsequent infections, the virus crosses the blood-brain barrier, infecting neurons and oligodendrocytes; viral replication peaks on days 5 to 7, and demyelination is observed between days 13 and 17. Myelin damage depends on the virus strain, the age of the carrier, and the developmental stage of the animal’s immune system.20

Japanese macaque encephalomyelitis (JME) is a demyelinating disease associated with a simian herpesvirus. It usually appears in young adult animals, independently of sex. It causes multiple foci of demyelination, with varying degrees of oligodendrocyte and axonal loss in the white matter of the brain, cerebellum, medulla oblongata, and spinal cord; these lesions are associated with macrophage and lymphocyte infiltration. Although JME and MS share certain clinical, imaging, and pathological features, they also have some differences, such as the numbers of neutrophils and lymphocytes in the CSF, and the presence of necrosis and haemorrhages in JME. Lesions in animals with JME may be acute or chronic.40,41

Mouse hepatitis virus is a coronavirus capable of inducing several diseases, depending on the strain. Intracranial or nasal infection with a neuroviral strain causes neurological disease. The disease develops in 2 stages; the first of these starts several days after infection and causes virus-induced panencephalitis. Animals subsequently recover, and the second stage starts 4 weeks later, with neuroparalytic disease associated with inflammatory demyelinating lesions. The virus is cleared from the brain at the end of the first stage, but viral RNA remains in tissues throughout the course of the disease.4,42

A major difference between viral models and EAE models is that virus-induced chronic inflammatory demyelination is associated with significant microglial activation.6
Models of demyelination and remyelination

Chemical lesion models
The agents most commonly used in these models are cuprizone, lyssolecithin, and ethidium bromide, all of which cause focal demyelination. The first 2 chemicals are used most frequently due to their ability to induce extensive demyelination in such CNS areas as the striatum, hippocampus, spinal cord, and optic nerve. Cuprizone is a chelating agent that is widely used due to its ability to induce CNS demyelination following systemic administration. It causes acute demyelinating lesions that may become chronic while cuprizone administration is continued. This model has the advantage that discontinuing administration triggers spontaneous remyelination, enabling the study of both processes. Furthermore, cuprizone causes T cell suppression, which enables the effects induced by immune system activation to be separated from those caused by the chemical compound in the study of demyelination and remyelination. Injection of lyssolecithin into the white matter causes focal demyelinating plaques, as the toxin damages the myelin sheath. The compound also acts as a chemoattractant to monocytes, triggering an inflammatory response; its effects can be observed in several experimental animals, including rats, mice, cats, and rabbits. As with other toxin-induced models of demyelination, the myelin damage stage is quickly followed by remyelination, although the speed and degree of remyelination are age-dependent. The toxicity of ethidium bromide is based on the compound’s interaction with DNA and mainly affects astrocytes: lesions are induced due to the lack of support factors released by these cells. This model has revealed that oligodendrocyte-mediated remyelination requires the presence of astrocytes.

Zebrafish model of myelination
The zebrafish is a small, relatively simple animal, which is optically transparent in the embryonic stage. Zebrafish embryonic development is fast: myelinated axons can be studied from the third day, enabling real-time, in vivo analysis of myelination and remyelination. Zebrafish reach sexual maturity very early, can produce hundreds of offspring, and are less costly to maintain than other experimental animals. Furthermore, they can be used to create transgenic lines expressing green fluorescent protein in oligodendrocytes and oligodendrocyte precursor cells, enabling the study of remyelination and testing of treatments promoting remyelination.

Transgenic animal models
Transgenic mice carrying insertions and deletions of genes coding for immune factors allow us to extrapolate the role of certain factors in the pathogenesis of CNS damage. Alterations similar to those observed in MS have been replicated in knockout animal models of several myelin proteins. Furthermore, myelination has been studied in various mutant mouse models of myelin deficiency, such as shiverer mice (in which the gene coding for MBP is duplicated and inverted), rumpshaker mice (mutation in the gene coding for PLP), and jimpy mice (point mutation in the gene coding for PLP); these mouse models all develop demyelination.

Conclusions
There is no specific model displaying the multiple factors involved in MS pathogenesis; researchers have therefore developed a wide range of models replicating various features of the disease. The development of new models or variations of existing models will contribute to a better understanding of the disease and its treatment. Animal models allow us to extrapolate information on treatment response. The development of models better able to reproduce the pathological changes of MS constitutes the first stage in the development of new treatments; however, we are most likely to gain true understanding of the disease through data from patients.

Chemical lesion models provide highly valuable information on demyelination and remyelination, but their results are not directly applicable. Selecting one model or another depends on a study’s specific aims.

Conflicts of interest
The authors have no conflicts of interest to declare.

References
1. Pachner AR. Experimental models of multiple sclerosis. Curr Opin Neurol. 2011;24:291—9.
2. Lassmann H, Bradl M. Multiple sclerosis: experimental models and reality. Acta Neuropathol. 2017;133:223—44.
3. Ben-nun A, Kaushanky N, Kawakami N, Krishnamoorthy G, Berer K, Liblau R, et al. From classic to spontaneous and humanized models of multiple sclerosis: impact on understanding pathogenesis and drug development. J Autoimmun. 2014;54:33—50.
4. Zhang H, Jarjour AA, Boyd A, Williams A. Central nervous system remyelination in culture—a tool for multiple sclerosis research. Exp Neurol. 2011;230:138—48.
5. Baker D, Jackson SJ. Model of multiple sclerosis. ACNR. 2007;6:10—2.
6. Van der Star BJ, Vogel DY, Kipp M, Puentes F, Baker D, Amor S. In vitro and in vivo models of multiple sclerosis. CNS Neurol Drug Targets. 2012;11:570—88.
7. Osorio-Querejeta I, Sáenz-Cuesta M, Muñoz-Culla M, Otaegui D. Models for studying myelination, demyelination and remyelination. Neuromol Med. 2017, http://dx.doi.org/10.1007/s12017-017-8442-1.
8. Duddy M, Haghikia A, Cocco E, Eggers C, Drulovic J, Carmona O, et al. Managing MS in a changing treatment landscape. J Neurol. 2011;258:728—39.
9. Nakahara J, Maeda M, Aiso S, Suzuki N. Current concepts in multiple sclerosis: autoimmunity versus oligodendrogliopathy. Clin Rev Allergy Immunol. 2012;42:26—34.
10. Matias-Guiu J, Gomez-Pinedo U, Matias-Guiu JA. News in multiple sclerosis: remyelination as a therapeutic target. Med Clin (Barc). 2017;148:377—80.
11. Gibbons HM, Dragunow M. Adult human brain cell culture for neuroscience research. Int J Biochem Cell Biol. 2010;42:844—56.
12. Majed HH, Chandran S, Niclou SP, Nicholas RS, Wilkins A, Wing MG, et al. A novel role for Sema3A in neuroprotection from injury mediated by activated microglia. J Neurosci. 2006;26:1730—8.
13. Peng W. Neuroprotective effects of G-CSF administration in microglia-mediated reactive T cell activation in vitro. Immunol Res. 2017, http://dx.doi.org/10.1007/s12026-017-8928-9.

14. Kipp M, van der Star B, Vogel D, Puentes F, van der Valk P, Baker D, et al. Experimental in vivo and in vitro models of multiple sclerosis: EAE and beyond. Mult Scler Relat Disord. 2012;1:15–28.

15. Gómez-Pinedo U, Sirerol-Piquer MS, Durán-Moreno M, García-Verdugo JM, Matías-Guiu J. Alexander disease mutations produce cells with coexpression of glial fibrillary acidic protein and NG2 in neosphere cultures and inhibit differentiation into mature oligodendrocytes. Front Neurol. 2017;8:255.

16. Madill M, Fitzgerald D, O’Connell K, Dev K, Shen S, FitzGerald U. In vitro and ex vivo models of multiple sclerosis. Drug Discov Today. 2016;21:1504–11.

17. Hurtado de Mendoza T, Balboa B, Slesinger PA, Verma IM. Organotypic cerebellar cultures: aptotic challenges and detection. J Vis Exp. 2011;51:2564, http://dx.doi.org/10.3792/jven.2564.

18. Rambani K, Vukasovic J, Glezer A, Potter SM. Culturing thick brain slices: an intrastill 3D microperfusion system for enhanced viability. J Neurosci Methods. 2009;180:243–54.

19. Constantinescu C, Farooqi N, O’Brien K, Gran B. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br J Pharmacol. 2011;164:1079–106.

20. Baker D, Amor S. Mouse models of multiple sclerosis: lost in translation? Curr Pharm Des. 2015;21:2440–52.

21. Haanstra K, Jaggers S, Bauchet A, Dossou M, Fovet C, Heijmans N, et al. Induction of experimental autoimmune encephalomyelitis with recombinant human myelin oligodendrocyte glycoprotein in incomplete Freund’s adjuvant in three non-human primate species. J Neuroimmunol Pharmacol. 2013;8:1251–64.

22. Mahfouz MM, Abdelsalam RM, Masoud MA, Mansour HA, Ahmed-Farid OA, Kenawy SA. The neuroprotective effect of mesenchymal stem cells on an experimentally induced model for multiple sclerosis in mice. J Biochem Mol Toxicol. 2017, http://dx.doi.org/10.1002/jbt.21936.

23. Procaccini C, de Rosa V, Puccino V, Formisano L, Matarese G. Animal models of multiple sclerosis. Eur J Pharmacol. 2015;759:181–91.

24. Haanstra KG, Dijkman K, Bashir N, Bauer J, Mary C, Poirier N, et al. Selective blockade of CD28-mediated T cell costimulation protects rhesus monkeys against acute fatal experimental autoimmune encephalomyelitis. J Immunol. 2015;194:1454–66.

25. Stimmer L, Fovet C, Serguera G. Experimental models of autoimmune demyelinating diseases in nonhuman primates. Vet Pathol. 2017, http://dx.doi.org/10.1177/0300983817712794.

26. Maggi P, Sati P, Massacesi L. Magnetic resonance imaging of experimental autoimmune encephalomyelitis in the common marmoset. J Neuroimmunol. 2017;204:86–92.

27. Kap Y, Jagessar A, Dunham J, Htart B. The common marmoset as an indispensable animal model for immunotherapy development in multiple sclerosis. Drug Discov Today. 2016;26:1200–5.

28. Starrsart E, Helms G, Garea-Rodriguez E, Nessler S, Hayardeny L, Wegner C, et al. A new targeted model of experimental autoimmune encephalomyelitis in the common marmoset. Brain Pathol. 2015;25:452–64.

29. Alberti TB, Barbosa WL, Vieira JL, Raposo NR, Dutra RC. (−)-β-Carophyllene, a CB2 receptor-selective phytocannabinoid, suppresses motor paralysis and neuroinflammation in a murine model of multiple sclerosis. Int J Mol Sci. 2017, http://dx.doi.org/10.3390/ijms18040691.

30. Amor S, Smith PA, Hart B, Baker D. Biozzi mice: of mice and human neurological diseases. J Neuroimmunol. 2005;165:1–10.

31. Bradl M, Misu T, Takahashi T, Watanabe M, Mader S, Reindl M, et al. Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. Ann Neurol. 2009;66:630–43.

32. Yao X, Su T, Verkman AS. Clbotesol promotes remyelination in a mouse model of neuromyelitis optica. Acta Neuropathol Commun. 2016;4:42.

33. Robinson A, Harp C, Noronha A, Miller S. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handb Clin Neurol. 2014;122:173–89.

34. Gambi D, di Cesare N, di Trapani G, Macchi G, Sbriccoli A. Experimental allergic encephalomyelitis in guinea pig: variability of response to intradural emulsion injection. Ital J Neurol Sci. 1989;10:33–41.

35. Kulikarni P, Yellanki S, Medishetti R, Siram D, Saxena U, Yogeesswari P. Novel Zebrfish EAE model: a quick in vivo screen for multiple sclerosis. Mult Scler Relat Disord. 2017;11:32–9.

36. Owens T. Animal models for multiple sclerosis. Adv Neurol. 2006;98:77–89.

37. McCarthy DP, Richards MH, Miller SD. Mouse models of multiple sclerosis: experimental autoimmune encephalomyelitis and Theiler’s virus-induced demyelinating disease. Methods Mol Biol. 2012;900:381–401.

38. Tsunoda I, Tanaka T, Terry EJ, Fujinami RS. Contrast roles for axonal degeneration in an autoimmune versus viral model of multiple sclerosis: what can axonal injury be beneficial? Am J Pathol. 2007;170:214–26.

39. DePaula-Silva AB, Hanak TJ, Libbey JE, Fujinami RS. Theiler’s murine encephalomyelitis virus infection of SJL/J and C57BL/6J mice: models for multiple sclerosis and epilepsy. J Neuroinmunol. 2017;308:30–42.

40. Axtheim M, Bourdette D, Marracci G, Su W, Mullaney E, Manoharan M, et al. Japanese macaque encephalomyelitis: a spontaneous multiple sclerosis-like disease in a nonhuman primate. Ann Neurol. 2011;70:362–73.

41. Blair TC, Manoharan M, Rawlings-Rhea KD, Tagge I, Kohama SG, Hollister-Smith J, et al. Immunopathology of Japanese macaque encephalomyelitis is similar to multiple sclerosis. J Neuroimmunol. 2016;291:1–10.

42. Bender S, Weiss S. Pathogenesis of murine coronavirus in the central nervous system. J Neuroimmunol Pharmacol. 2010;5:336–54.

43. Woodruff RH, Franklin RJ. Demyelination and remyelination of the caudal cerebellar peduncle of adult rats following stereotaxic injections of lysolecithin, ethidium bromide, and complement/antigalactocerebroside: a comparative study. Glia. 1999;25:216–28.

44. Peraat J, Guglielmetti C, Berneman Z, van der Linden A, Ponsaerts P. Cellular and molecular neuropathology of the cuprizone mouse model: clinical relevance for multiple sclerosis. Neurosci Biobehav Rev. 2014;47:485–505.

45. Blakemore WF, Franklin RJ. Remyelination in experimental models of toxin-induced demyelination. Curr Top Microbiol Immunol. 2008;318:193–212.

46. Jeffery N, Blakemore W. Remyelination of mouse spinal cord axons demyelinated by local injection of lysolecithin. J Neurocytol. 1995;24:775–81.

47. Merrill J. In vitro and in vivo pharmacological models to assess demyelination and remyelination. Neuropsychopharmacology. 2009;34:55–73.

48. Preston MA, Macklin WB. Zebrash fish as a model to investigate CNS myelination. Glia. 2015;63:177–93.

49. Ackerman SD, Monk KR. The scales and tales of myelination: using zebrash and mouse to study myelinating glia. Brain Res. 2016;1641:79–91.

50. Gong Z, Ju B, Wan H. Green fluorescent protein (GFP) transgenic fish and their applications. Genetica. 2001;111:213–25.

51. Dubińska-Magiera M, Daczwiska M, Lewicka A, Migocka-Patrzalek M, Niedbalska-Tarnowska J, Jagla K. Zebrash: a model for the study of toxicants affecting muscle function.
development and function. Int J Mol Sci. 2016, http://dx.doi.org/10.3390/ijms17111941.
52. Kirby BB, Takada N, Latimer AJ, Shin J, Carney TJ, Kelsh RN, et al. In vivo time-lapse imaging shows dynamic oligodendrocyte progenitor behavior during zebrafish development. Nat Neurosci. 2006;9:1506–11.
53. Udvadia AJ, Linney E. Windows into development: historic, current, and future perspectives on transgenic zebrafish. Dev Biol. 2003;256:1–17.
54. Buckley CE, Goldsmith P, Franklin RJ. Zebrafish myelination: a transparent model for remyelination? Dis Model Mech. 2008;1:221–8.