Brain Research 1648 (2016) 594–602

Contents lists available at ScienceDirect

Brain Research

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

Review

Endoplasmic reticulum stress and the unfolded protein response in disorders of myelinating glia

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ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form
25 March 2016
Accepted 26 March 2016
Available online 4 April 2016

Keywords:
ER stress
Unfolded protein response
Myelin
Oligodendrocytes
Schwann cells

ABSTRACT

Myelin is vital to the proper function of the nervous system. Oligodendrocytes in the CNS and Schwann cells in the PNS are the glial cells responsible for generating the myelin sheath. Myelination requires the production of a vast amount of proteins and lipid-rich membrane, which puts a heavy load on the secretory pathway of myelinating glia and leaves them susceptible to endoplasmic reticulum (ER) stress. Cells respond to ER stress by activating the unfolded protein response (UPR). The UPR is initially protective but in situations of prolonged unresolved stress the UPR can lead to the apoptotic death of the stressed cell. There is strong evidence that ER stress and the UPR play a role in a number of disorders of myelin and myelinating glia, including multiple sclerosis, Pelizaeus-Merzbacher disease, Vanishing White Matter Disease, and Charcot-Marie-Tooth disease. In this review we discuss the role that ER stress and the UPR play in these disorders of myelin. In addition, we discuss the progress that has been made in our understanding of the effect genetic and pharmacological manipulation of the UPR has in mouse models of these disorders and the novel therapeutic potential of targeting the UPR that these studies support.

This article is part of a Special Issue entitled SI:ER stress.

Contents

1. Introduction

Oligodendrocytes of the central nervous system (CNS) and Schwann cells from the peripheral nervous system (PNS) are glia cells responsible for producing the myelin sheath that wraps axons (Fig. 1). Myelin is a multi-lamellar structure that wraps axons in multiple layers of compact lipid membrane with a cytoplasmic channel next to the periaxonal space. Oligodendrocytes simultaneously myelinate multiple axonal segments while Schwann cells myelinate a single segment of axon. The original function attributed to the myelin sheath was simply that of an electrical insulator to promote fast conduction of action potentials by increasing electrical resistance and decreasing capacitance (Bercury and Macklin, 2015). Nevertheless, myelin is also essential in establishing the nodes of Ranvier, paranodes, and juxtaparanodes - axonal domains which are necessary for saltatory conduction (Fig. 2) (see Buttermore et al. (2013) for review). The presence of

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http://dx.doi.org/10.1016/j.brainres.2016.03.046
0006-8993/

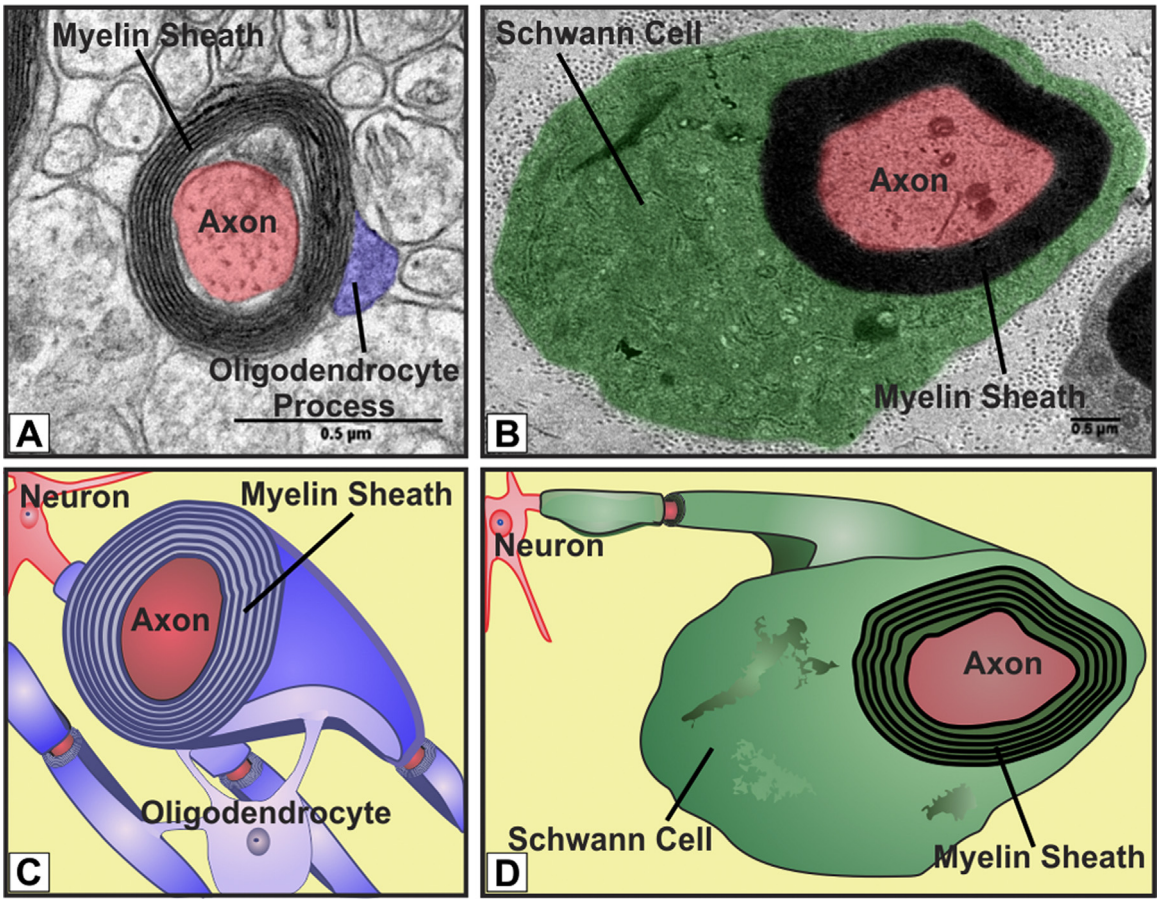

Fig. 1. Oligodendrocyte and Schwann cell electron micrographs. (A) False color electron microscopy image and (C) schematic of a myelinated axon in the CNS with an oligodendrocyte process (blue) forming the myelin sheath. Oligodendrocytes will myelinate multiple axon segments in the CNS. (B) False color electron microscopy image and (D) schematic of a myelinated axon in the PNS. The Schwann cell body (green) engulfs the axon and will only produce the myelin sheath for a single axon segment.

myelinating glia is necessary for clustering of sodium channels within the axonal membrane at nodes of Ranvier (Ching et al., 1999; Rasband et al., 1999) and potassium channels at the juxtaparanode region (Fig. 2) (Baba et al., 1999). Moreover, myelin and myelinating glia are critical for the development and maintenance of axonal integrity through metabolic support (see Simons and Nave (2015) and Morrison et al. (2013) for review). Disruption of certain oligodendrocyte proteins can lead to axonal pathology even in the absence of gross demyelination. For example, ablation of the oligodendrocyte specific protein 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNP) in mice causes axonal damage such as axonal swelling, despite the presence of compact myelin (Griffiths et al., 1998; Lappe-Siefke et al., 2003). In addition, myelinating glia play an important role in providing metabolic energy to the axon through the myelin sheath. Although local energy production along the axon is likely necessary to maintain proper function, compact myelin covers much of the axonal surface area, thus limiting access of the axon to extracellular glucose for energy production. Recent findings indicate that myelinating glia act as energy providers via monocarboxylate transporters (MCTs) transport lactate and pyruvate across the cell membrane. MCT1 is localized to oligodendrocytes while MCT2 is found in neurons (Lee et al., 2012; Rinholm et al., 2011). Importantly, oligodendrocyte-specific downregulation of *Mct1* causes axonal pathology (Lee et al., 2012) without death of oligodendrocytes which is likely due to the ability of oligodendrocytes to survive on aerobic glycolysis (Fünfschilling et al., 2012). These results suggest a system in which lactate, a product of glycolysis, is transported from myelin to axons via MCT1 and MCT2, such that myelinating glia provide metabolic support for axons isolated from extracellular glucose (Fig. 2). The dependence on myelinating glia for formation of axonal domains and metabolic support clearly demonstrate that myelin is more than a passive electrical insulator. Indeed, myelination has been shown to be a major step in the evolution of the vertebrate nervous system with critical roles in motor, sensory, and cognitive function (Bercury and Macklin, 2015).

The importance of myelin and myelinating glia is unmistakable given the devastating effects of disorders of myelin including multiple sclerosis (MS), Pelizaeus-Merzbacher disease (PMD), Vanishing White Matter Disease (VWMD), and Charcot-Marie-Tooth disease (CMT) (Table 1). MS is a common CNS demyelinating disorder involving T cell-mediated autoimmunity that results in inflammation, loss of oligodendrocytes, demyelination, and axonal damage leading to worsening neurological outcomes that significantly decrease quality of life (Franklin et al., 2012). PMD is a genetic demyelinating disorder of the CNS with childhood onset caused by mutations in the *PLP1* gene, which encodes proteolipid protein (PLP), a major protein component of myelin; prognosis varies by mutation from gait abnormalities to progressive neurological decline until death (Garbern, 2007). VWMD is an autosomal-recessive disorder characterized by CNS hypomyelination and abnormal "foamy" oligodendrocytes that occurs following minor head trauma or febrile infection causing episodes of rapid and progressive neurological deterioration (Van der Knaap et al., 2006). CMT is a genetic disorder that affects PNS myelin and one form, CMT1, is caused by dominant mutations in genes that encode peripheral myelin proteins. CMT affects both motor and sensory nerves but is not fatal (Theocharopoulou and Vlamos,