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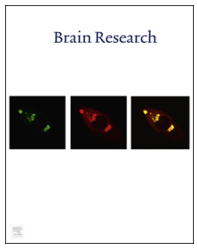

Review

The scales and tales of myelination: using zebrafish and mouse to study myelinating glia

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ABSTRACT

Myelin, the lipid-rich sheath that insulates axons to facilitate rapid conduction of action potentials, is an evolutionary innovation of the jawed-vertebrate lineage. Research efforts aimed at understanding the molecular mechanisms governing myelination have primarily focused on rodent models; however, with the advent of the zebrafish model system in the late twentieth century, the use of this genetically tractable, yet simpler vertebrate for studying myelination has steadily increased. In this review, we compare myelinating glial cell biology during development and regeneration in zebrafish and mouse and enumerate the advantages and disadvantages of using each model to study myelination.

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Contents

Abbreviations: aGPCR, adhesion G protein-coupled receptor; BL, basal lamina; cAMP, 3′,5′-cyclic monophosphate; CRISPR-Cas, clustered regularly interspaced short palindromic repeats-CRISPR associated; CTF, C-terminal fragment; dpf, days post-fertilization; E, embryonic day; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolytic site; hpf, hours post-fertilization; indel, insertion and deletion; mpf, months post-fertilization; NTF, N-terminal fragment; OL, oligodendrocyte; OPC, oligodendrocyte precursor cell; PKA, protein kinase A; pLLn, posterior lateral line nerve; SC, Schwann cell; TALENs, transcription activator-like effector nucleases

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1. Introduction

Over the course of evolutionary history, vertebrates experienced a dramatic increase in body size. Because the speed at which an action potential propagates along an axon is directly proportional to axon diameter, large increases in body size could be facilitated by a subsequent increase in axon diameter. Indeed, this compensation is observed in large invertebrate species including cephalopods, whose axons can reach several millimeters in diameter (Zalc and Colman, 2000). However, the emergence of larger, more complex vertebrate species with dermal skeletons encasing the nervous system (thereby restricting continued increase in axon diameter) required additional means for ensuring proper nerve conduction velocity (Zalc et al., 2008; Zalc, 2016). To facilitate this increase in body size, the vertebrate nervous system adapted to produce specialized glial cells that could insulate regular intervals (internodes) along large caliber axons. This insulation, in the form of myelin generated by Schwann cells (SCs) in the peripheral nervous system (PNS) and oligodendrocytes (OLs) in the central nervous system (CNS), prompted saltatory conduction between ion channels clustered at the nodes of Ranvier rather than continuous membrane depolarization, which is both energetically unfavorable and slow (Nave, 2010). Therefore, the development of myelin was likely essential for the expansion and evolutionary success of vertebrates by enabling rapid nerve conduction velocity in a confined space.

Although myelin is an innovation of the jawed-vertebrate lineage, myelin biology has been primarily studied in mammalian model systems with particular emphasis on rodent models (Bullock et al., 1984; Zalc et al., 2008; Schweigreiter et al., 2006). In the past few decades, zebrafish (*Danio rerio*) have emerged as a powerful vertebrate model system; external fertilization, large brood size, and the optical clarity of zebrafish embryos are just a few of the advantages of using this model to study development (Driever et al., 1994). Zebrafish belong to the jawed-vertebrate lineage and therefore represent a more simple and accessible genetically tractable organism for studying the development of myelinating glial cells. Indeed, within the past ~10 years, numerous studies have demonstrated that zebrafish can be used to elucidate essential and evolutionary conserved pathways that regulate both SC and OL myelination (Lyons and Talbot, 2015; Preston and Macklin, 2015). In this review, we will summarize similarities and differences between SC and OL development and myelination in zebrafish and mouse, discuss how these differences impact CNS remyelination, and highlight the strengths and weaknesses of each model system for the study of myelinating glia.

2. Schwann cell development and myelination

In the PNS, myelin is formed from neural crest-derived SCs that sort and associate with single axonal segments in a 1:1 SC:axon segment relationship (Jessen and Mirsky, 2005; Monk et al., 2015; Feltri et al., 2015). The timing and expression of essential molecular markers governing each stage of SC development are well described and are remarkably conserved between mouse and zebrafish (Fig. 1). In both species, neural crest cells expressing *Sox9* and *Sox10* delaminate from the neural tube during early embryonic development (embryonic day (E) 8.5 in mouse, 12.5 h post-fertilization (hpf) in zebrafish) and migrate into the periphery (Kelsh, 2006; Klymkowsky et al., 2010; Erickson and Weston, 1983). SC precursors expressing *Erbb2* and *Erbb3* develop from a subset of migrating neural crest cells (E12-13 in mouse, 18–48 hpf in zebrafish) and continue to co-migrate along path finding axons (Jessen and Mirsky, 2005; Gilmour et al., 2002; Lyons et al., 2005). As SC precursor migration terminates, the newly formed immature SCs encompass bundles of axons, interdigitate cytoplasmic processes into the bundle, and separate axons according to their size in a process called radial sorting (initiating ~E13-15 in mouse and ~48 hpf in zebrafish) (Jessen and Mirsky, 2005; Raphael et al., 2011; Feltri et al., 2015). Small caliber axons that express low levels of axon-derived Neuregulin I type III remain unmyelinated; however, bundles of small caliber axons are encompassed by the cytoplasm of non-myelinating (Remak) SCs in mature nerves. Conversely, segments of large caliber axons, approximated by high levels of Neuregulin I type III, are sorted into a 1:1 relationship with a promyelinating SC expressing *Oct6/Pou3f1* and *Krox20/Egr2* (initiating ~E15 in mouse and ~48 hpf in zebrafish). At this point, the future internode is wrapped 1–1.5 times by the promyelinating SC, but is not yet myelinated (Michailov et al., 2004; Taveggia et al., 2005; Jessen and Mirsky, 2005; Raphael et al., 2011). Once sorted, terminal differentiation of promyelinating SCs into myelinating SCs ensues (initiating perinatally in mouse and ~60 hpf in zebrafish), accompanied by vast morphological changes, upregulation of key myelin genes, and a dramatic increase in lipid synthesis (Jessen and Mirsky, 2005; Brösamle and Halpern, 2002; Raphael et al., 2011; Chrast et al., 2011; Monk et al., 2015).

One essential regulator of SC development is the adhesion class G protein-coupled receptor (aGPCR) Gpr126/Adgrg6, which was first discovered in zebrafish. Starting with a forward genetic screen for mutations that affect the development of myelinated axons (Pogoda et al., 2006), it was determined that Gpr126 is an evolutionarily conserved