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Understanding Schwann cells: new insights into the developing peripheral nervous system

Our study focuses on signals that control the development and function of Schwann cells, which are glial cells that reside in the peripheral nervous system (PNS). Schwann cells sort axons, surround the axons and form a myelin sheath, which acts as an electrical insulator of the axon. This ensures that the nerve fiber can transfer an impulse or signal with alarming celerity. Schwann cells also provide metabolic support to axons. In addition to their role in developmental myelination, Schwann cells are responsible for repair and remyelination of the PNS following injury

During the radial axonal sorting process, which takes place around birth, immature Schwann cells extend cytoplasmic processes to axon bundles and initiate the sorting of axons based on size. Schwann cells establish a one to one ratio with large caliber axons and subsequently myelinate them. Small caliber axons remain as bundles (known as Remak bundles) and are surrounded by non-myelinating Schwann cells.

The goal of our study was to shed new light on the molecular mechanisms that govern the radial axonal sorting and myelination processes in the PNS. Specifically, we examined the role Adenomatous Polyposis Coli (APC) plays in Schwan cells. We were interested in APC because this protein modifies an indispensable transcription pathway: the Wnt/β-catenin pathway. β-catenin is constantly present in the cell, but is inactive due to binding by an inhibitory complex consisting of the proteins APC, GSK3, and Axin2. Collectively, these three proteins are known as the β-catenin destruction complex as they promote the proteolysis and destruction of β-catenin. When the Wnt signaling pathway is activated, β-catenin dissociates from the destruction complex, upon which it can enter the nucleus, bind to and activate transcription factors, and promote the transcription of specific genes.

We used the Cre-Lox recombinase system to create a mouse model system in which APC was ablated specifically in Schwann cells. The mutant mice had weaker hindlimbs, a reduced grip strength, and slower electrical signal transmission in their sciatic nerves. Electron microscopy analysis demonstrated that myelin production was delayed in mice without APC. The thickness of the myelin sheath (g-ratio) and the length of the internodes, which are important indicators of how well action potentials can propagate down axons, were reduced in the mutated mice. The observed delay in myelination in the mutated mice was a result of delayed differentiation of Schwann cells.

We also observed perturbed axonal sorting in the sciatic nerves; the APC knockout mice had larger bundles of unmyelinated axons that contained both large and small caliber axons. This indicates that the APC-deficient Schwann cells were unable to appropriately distinquish between the small and large axons during radial axonal sorting.

APC is a multi-functional protein which, in addition to its role in the Wnt/β-catenin signal transduction pathway, also plays a role in the cell cytoskeleton. In our experiments, APC colocalized with actin, tubulin, and lamellipodia, which is an actin-based structure that plays a crucial role in axonal sorting. Previous studies have shown that the activation of the Wnt/β-catenin signal transduction pathway results in heightened lamellipodia formation (Grigoryan et al., 2013); APC loss, as expected, also resulted in

increased lamellipodia formation (Elbaz et al., 2016). This was further examined by either inhibiting or activating the other components of the destruction complex pharmacologically: when Wnt signaling was activated, lamellipodia formation was correspondingly increased, and when Wnt signaling was inactivated, lamellipodia formation was decreased. Interestingly, cell process extension was not affected by any of the drugs, which demonstrates that not all of the effects observed in APC knockout mice are related to the Wnt/β-catenin pathway.

Our data indicate that APC is important for timely Schwann cell differentiation, lamellipodia formation, cell process extension, and hence, for radial axonal sorting and myelination of the PNS (Elbaz et al., 2016). Through studying the molecular mechanisms by which developmental myelination occurs and is disrupted, we have expanded our knowledge on the molecular cues controlling PNS myelination. This knowledge will be crucial in our attempts to pharmacologically intervene and enhance myelination in the PNS.

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Publications

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