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Anti-TANKyrase weapons promote myelination

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Abstract

A study identifies mechanisms responsible for the inability to form new myelin after neonatal hypoxia. It identifies Axin2 as a potential therapeutic target for reversing the ‘differentiation block’ of oligodendrocyte-lineage cells.

Cerebral palsy and cognitive deficits represent the devastating consequences of preterm births and of perinatal hypoxic or ischemic injury of full-term infants. At a cellular level, disease severity correlates with the degree of white matter injury and is characterized by the inability of cells in the oligodendrocyte lineage to differentiate into myelin-forming cells. There are no therapies to overcome this differentiation block. A similar deficit in the ability to form new myelin can be detected in the adult brain after demyelination in people with multiple sclerosis and is associated with lack of repair. In this issue of *Nature Neuroscience*, Fancy and colleagues¹ identify Axin2, an inhibitor of the Wnt pathway, as a promising new therapeutic target for drug development directed at favoring new myelin formation in the neonatal and adult brain.

Wnt proteins comprise a family of secreted ligands crucial for stem cell biology and embryonic development. Inappropriate regulation of Wnt signaling occurs in several types of cancer, including colon, liver and brain tumors of neuroectodermal origin, and involves a downstream molecule called β -catenin. In the absence of Wnt, Axin1 cooperates with glycogen synthase kinase 3 (GSK3) and phosphorylates β -catenin, thereby signaling its degradation. In the presence of Wnt, β -catenin is not phosphorylated and accumulates in the cell and modulates gene expression. Active Wnt has been shown to impair oligodendrocyte progenitor differentiation and repair of demyelination^{2–5}.

Fancy and colleagues¹ identified the protein Axin2, also known as Axil (in rat) and Conductin (in mouse), as a negative regulator of β -catenin stability (Fig. 1), even in the presence of Wnt signaling. *Axin2* transcripts require β -catenin⁶, and *Axin2* transcripts are detected at high levels in genetically engineered mice with active Wnt signaling and impaired differentiation of oligodendrocyte-lineage cells¹. *Axin2* transcripts are also detected in oligodendrocyte progenitors, but not in mature oligodendrocytes or astrocytes, in the brain of infants with hypoxic damage of the white matter, but not in unaffected controls. Thus, *Axin2* transcripts decline as progenitors differentiate in physiological conditions, but persist in oligodendrocyte-lineage cells that are unable to form myelin.

What is the role of Axin2? Studies conducted in mice and in cultured progenitors lacking *Axin2* found myelination delays during development and impaired myelin repair in adult mice with chemically induced demyelination. Thus, the function of Axin2 is not redundant with Axin1. Axin2 function is critical for oligodendrocyte differentiation, but its transcript levels are elevated in cells that are unable to myelinate. How can the same molecule be downstream of a signal that negatively modulates myelin formation and still be necessary for oligodendrocyte maturation? This conundrum can be explained in terms of the mechanisms regulating Axin2 protein abundance. A feature of many signaling components of the Wnt pathway is their regulation by proteolytic degradation. In the absence of Wnt, β -catenin is retained in the cytosol, where it is phosphorylated by GSK3 and degraded (Fig. 1). In the presence of Wnt, β -catenin is stable and translocates to the nucleus, where it forms an activating complex with TCF/LEF transcription factors and modulates the expression of several genes, including *Axin2* (ref. 6). Under physiological conditions, Axin2 protein negatively regulates this signaling pathway by promoting the degradation of β -catenin even in the presence of Wnt, possibly through a GSK3-mediated mechanism that is critical for oligodendrocyte differentiation⁷. The authors therefore suggest that, although detection of *Axin2* transcripts is indicative of Wnt signaling, the detection of Axin2 protein reveals efficient negative feedback.

In the absence of Wnt, β -catenin degradation is dependent on phosphorylation. In the presence of Wnt, Axin2 degradation is dependent on poly(ADP-ribosylation) (PARsylation). This modification consists of the addition of ADP-ribose groups to the molecule by enzymes called tankyrases. Protein PARsylation has also been described in the regulation of telomeres and of the mitotic spindle^{8–10} and has been identified as a recognition signal for E3 ubiquitin ligases to target proteins to the degradation pathway¹¹. In the brains of newborns with white-matter damage, the concurrent expression of *Axin2* mRNA and of tankyrases in oligodendrocyte-lineage cells suggest that low levels of Axin2 protein might be responsible for the lack of new myelin. The importance of Axin2 PARsylation for myelin formation was supported by the evidence that XAV939, a pharmacological inhibitor of tankyrases¹², substantially enhanced myelin regeneration after demyelination in wild-type mice, but not in *Axin2*-null mice. The small molecule XAV939 also favored new myelin formation in slice cultures damaged by exposure to low oxygen, suggesting that it could represent a therapeutic target for conditions associated with cerebral palsy and cognitive deficits caused by hypoxia-ischemia or by premature birth.

Although promising, these results leave several questions unanswered. One of the most critical is whether the tankyrase inhibitor is able to effectively reverse the differentiation block detected in animal models of hypoxia-ischemia. The brain is a more complex environment than a brain slice in a dish, and additional pathways and interactions among distinct cell types and with the vasculature and extracellular matrix could further modulate Axin2 function. Crosstalk among pathways that negatively affect myelinogenesis could further amplify the differentiation block of progenitors. It is also likely that acute injury during a critical developmental window *in vivo* may lead to epigenetic changes in the target cells¹³ and preclude responsiveness to treatment.

New studies on the mechanism of tankyrase regulation through bioavailability and modulation of enzymatic activity will inform potential new therapeutic strategies for myelin regeneration. In addition, tankyrases are not the only target of XAV939, and *in vivo* treatment could favor myelination by indirect modulation of other substrates. Finally, the detection of *Axin2* mRNA in the brains of adults with multiple sclerosis and in mice with chemically induced demyelination suggests that the Wnt/Axin2/ β -catenin signaling pathway may act in any condition associated with myelin damage and subsequent repair and identifies tankyrases as promising therapeutic targets.

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Figure 1.

Modulation of Wnt signaling in oligodendrocyte-lineage cells. Active Wnt signaling in progenitor cells is characterized by active β -catenin (*) and induction of target genes, including *Axin2*, which in turn acts as a negative regulator of β -catenin. *Axin2* protein stability is further regulated by tankyrase enzymes, which are responsible for adding poly(ADP-ribose) groups (ADPr_n) and signaling degradation. In differentiating oligodendrocytes Wnt signaling is low in physiological conditions, but persists in pathological conditions associated with perinatal hypoxia-ischemia. In these cases, inhibitors of tankyrases (XAV939) can be used to stop *Axin2* degradation and favor oligodendrocyte differentiation.