In sum, Yuen et al. (2014) propose that perinatal OPC-expressed HIF promotes angiogenesis but arrests OPC differentiation, acting through Wnt7 in a paracrine and autocrine fashion, respectively. Once the microvasculature is established, oxygen levels exert negative feedback on HIF activity, disinhibiting OPC maturation only when its metabolic demands can be met. Myelination failure could therefore arise from constitutively low HIF activity in OPCs, where white matter is hypovascular and nonviable, or persistently high HIF activity and angiogenic failure, which prevent OPC differentiation. This novel feedback loop implies that the onset of myelination is coordinated locally and that any attempt to understand developmental myelination must consider the "oligovascular" microenvironment.

The involvement of HIF in postnatal myelination lends itself to many exciting questions. First, this model shows that myelination success depends on timely changes in OPC HIF activity levels. Would myelination then proceed at different rates, or at different oxygen thresholds, in brain regions experiencing different oxygen tensions? Second, what is the critical window in which changes to HIF activity could influence myelination? Third, would pathological processes that

modify HIF activity in qualitatively different ways—such as acute, as opposed to chronic or intermittent, hypoxia—affect postnatal myelination differently? Fourth, do oxygen-independent modifiers of HIF activity, including PI3K/Akt, mTOR, NFκB, and SIRT1, also affect myelination? Finally, given the ubiquity of HIF, it is tempting to speculate that HIF-mediated crosstalk may be relevant to other glial cell types.

After the perinatal stage, OPCs are also found in the adult brain, arising in the subventricular zone. These OPCs are activated following demyelination, such as in mechanical trauma or inflammation. It will be critical to discover now whether differentiation of adult and perinatal OPCs is similarly regulated and, if so, whether a HIF/Wnt7a/7b pathway is applicable to our understanding of remyelination in multiple sclerosis, spinal cord injury, stroke, or vascular dementia. Encouragingly, in an adult rat ischemic stroke model, areas with the highest OPC maturation rates were found to have the highest vessel densities (Jiang et al., 2011). Together with other emerging data, this suggests that the relevance of the "oligovascular" crosstalk described in the present work may extend beyond the developmental milieu.

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A Long Noncoding Way to Alternative Splicing in Plant Development

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In this issue of *Developmental Cell*, Bardou et al. (2014) elucidate how long, highly structured noncoding RNAs control alternative splicing regulators that specifically mediate the action of the hormone auxin in the promotion of lateral root growth in *Arabidopsis*.

Plants and animals share more features than generally appreciated. Beyond having in common basic genetic mechanism, overall cellular structure, and most biochemical reactions, both plants and an-

imals have genes containing introns that are removed through nuclear pre-mRNA splicing. The splicing machinery is mostly conserved between plant and animal cells: the RNA sequences defining exon/intron

boundaries, spliceosome components, and splicing factors primarily characterized in mammalian cells are also present in plants. Nevertheless, there are differences. Plant introns are, on average,

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shorter than their animal counterparts, and whereas intron retention is the most common alternative splicing event in plants, cassette exons prevail in animals. The number of genes encoding SR proteins, the best-character-ized splicing regulators, is also higher in plants (18 in *Arabidopsis thaliana* com-pared to 12 in humans) (Reddy et al., 2013). Although the per-centage of *Arabidopsis* genes whose transcripts are af-fected by alternative splicing (60%) (Márquez et al., 2012) is smaller than that in humans (95%) (Barash et al., 2010), both numbers are high enough to warrant the conclu-sion that alternative splicing is a main contributor to expand-ing the repertoire of tran-scripts and proteins encoded by the corresponding genomes. Several plant studies indicate that both biotic and abiotic stresses, along with environmental cues such as light (Petrillo et al., 2014), affect splicing decisions and that alterna-tive splicing is important for photosyn-thesis, defense responses, flowering, and the circadian clock (Reddy et al., 2013).

In a study published in the current issue of *Developmental Cell*, Bardou et al. (2014) define precise roles and regulatory mechanisms for alternative splicing in *Arabidopsis* and, in the process, implicate a role of long noncoding RNAs (lncRNAs), thus greatly contributing to shortening the gap between the understanding of plant and animal alternative splicing. Bardou et al. (2014) focused on the *Arabidopsis* alternative splicing regulators AtNSR a and b, originally identified in the legume *Medicago truncatula*. Members of the NSR family of alternative splicing regula-tors normally localize within nuclear com-partments known as speckles. Nuclear speckles exist in both animal and plant cells and are usually considered to be splicing factor reservoirs where alterna-tive and constitutive splicing factors, as well as other regulatory molecules, shuttle to and from. *AtNSRa/b* expression occurs specifically in root meristems and lateral roots, consistent with the fact that the *nsra/nsrb* double mutant has fewer and shorter lateral roots and is less sensitive
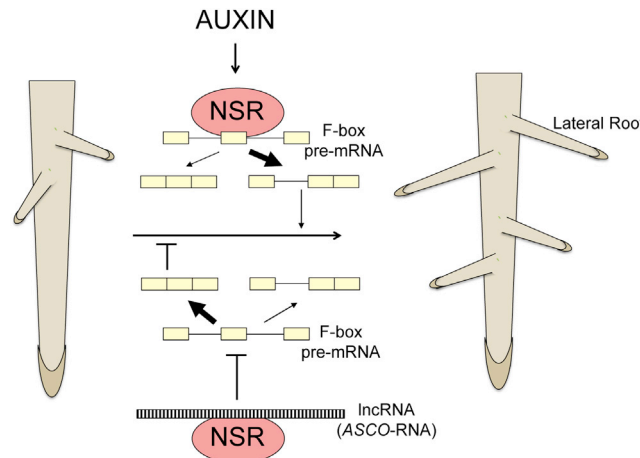
Figure 1. Antagonistic Roles of Auxin and lncRNAs in the Promotion of Lateral Root Growth
Intron retention in the example alternative splicing event of the mRNA encod-ing the F-box protein *At4G27050* is stimulated by auxin via NSR binding, which in turn stimulates lateral root growth. Expression of the lncRNA *ASCO*-RNA displaces NSR from its target sequence and changes alternative splicing to the mRNA isoform that does not retain the intron, conditions that do not promote lateral root growth.

to the stimulation of lateral root growth by the plant hormone auxin. Bardou et al. (2014) showed that auxin action in this context involves the regulation of a set of alternative splicing events in 85 of the 288 genes tested, a vast majority of which required the NSR proteins. A role for alter-native splicing regulators that specifically mediate the action of a hormone on a defined set of transcripts with morpholog-ical consequences is a beautiful and important result with no clear parallels in the regulation of alternative splicing in ani-mal cells. The authors then uncovered a second level of regulation of NSR proteins by long noncoding RNAs. In previous work, carried out in *Medicago truncatula*, this group had characterized a highly structured long RNA with poor protein coding capacity, named *ENOD40*, which allowed them to isolate the first NSR pro-tein (MtNSR) due to its ability to bind to *ENOD40*. Subsequently, they found that *ENOD40* overexpression caused the re-localization of MtNSR from speckles to the cytoplasm. In the present report, the authors not only confirm the existence of an ortholog *NSR* in *Arabidopsis* but also show that relocalization of both AtNSRs from nuclear speckles to the cytoplasm upon interaction with *ENOD40* affects the patterns of the NSR-dependent alternative splicing events, presumably due to NSR nuclear depletion. Interestingly, they also

find an *Arabidopsis* lncRNA able to bind the NSR factors, which they named *ASCO-RNA*. *ASCO-RNA* expression is upregulated in the *nsra/nsrb* double mutant, which sug-gests that NSRs not only affect the patterns of alternatively spliced mRNA isoforms but also regulate, directly or indi-rectly, the expression of lncRNAs. *ASCO-RNA* controls NSR-dependent alternative splicing events as well, but through a different mecha-nism. Bardou et al. (2014) found that this lncRNA does not cause NSR relocalization but alters NSR activity through direct binding to NSRs and dis-placement of them from their mRNA targets. In other words, *ASCO-RNA* prevents the ef-fects of NSRs on the regulation of alternative splicing in their transcript targets. Consistent with this, the authors show that *ASCO-RNA* overex-pression in live plants duplicates the morphological effects observed in the *nsra/nsrb* double mutant, i.e., a decreased lateral root density when plants are grown on auxin (Figure 1).

There is increasing evidence for par-ticipation of noncoding RNAs in the regu-lation of splicing through at least two different mechanisms. At the chromatin modification level, small interfering RNAs and argonaute proteins (Alló et al., 2009; Ameyar-Zazoua et al., 2012) have been shown to drive the "writing" of intragenic silencing histone marks, which regulate alternative splicing through the control of Pol II elongation. DICER, another compo-nent of the small RNA pathway, has recently been shown to play a role in the nucleus, in addition to its well-character-ized cytoplasmic role in posttranscrip-tional gene silencing (White et al., 2014). At the level of direct interaction with splicing regulators, as in the cases of *ENOD40* and *ASCO-RNA*, the mamma-lian lncRNA MALAT1 is located in speckles and modulates the localization of several splicing factors and their phos-phorylation status (Tripathi et al., 2010). Also, the splicing factor TDP43 seems to be sequestered by the ncRNAs MALAT1 and NEAT1 in the brain cells of individuals with frontotemporal lobar degeneration,

where the level of these transcripts is augmented (Tollervey et al., 2011). The binding of all of these lncRNAs to splicing factors seems to require little or no sequence specificity on the lncRNA side but rather depends on the highly structured nature of the RNAs. Therefore, *ENOD40* and *ASCO-RNA* could be seen as silent partners, able to redistribute or hijack alternative splicing factors, diverting them from their primary targets, a mechanism whose generalization in eukaryotes deserves further exploration.

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