SIGNALING

A Norrin trio

Genes Dev. **27**, 2305–2319 (2013)

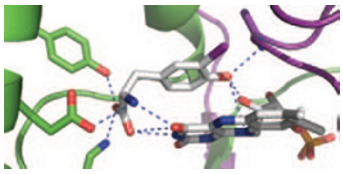
Norrin is a cystine knot growth factor that interacts with the Frizzled 4 (Fz4) receptor and the Wnt co-receptor LRP5/6 to activate β-catenin signaling, thereby regulating diverse developmental processes such as angiogenesis and eye and ear development. However, the exact role of LRP5/6 in promoting Norrin-mediated signaling has remained unclear owing to the inability to detect its direct biochemical interactions. Ke *et al.* used a maltose binding-protein–Norrin fusion protein (Norrin-MBP), which improved solubility and aided purification, to isolate pure proteins in sufficient yield to obtain a crystal structure at 2.4-Å resolution. In addition to the cystine knot in each monomer, the structure showed a Norrin dimer stabilized by three intermolecular disulfide bonds and a hydrophobic surface. Disruption of these bonds or the hydrophobic interface resulted in a loss of Norrin-mediated signaling. The use of the fusion protein also enabled the authors to detect the direct binding of Norrin-MBP to the extracellular domains of LRP5/6, whereas competition assays revealed that Fz4 and LRP56 bind distinct sites on Norrin. Furthermore, the authors identified LRP5/6 binding sites on Norrin that, when mutated, did not affect Fz binding but decreased Norrin signaling activity. Finally, the presence of Norrin promoted the immunoprecipitation of Fz4 with LRP5, suggesting that Norrin requires direct interactions with both Fz4 and LRP5/6 to activate downstream mediators. *GM*

ENZYMES

I branches out

Mol. Biosyst.; doi:10.1039/c3mb70398c

ABHISHEK PHATARPHEKAR



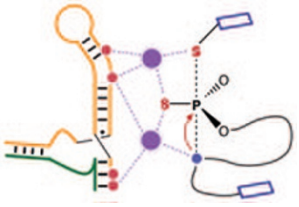
Thyroid hormone is a multiply iodinated, tyrosine-based molecule that regulates metabolism. Iodotyrosine deiodinase (IYD) takes part in thyroid hormone synthesis by salvaging iodide from mono- and diiodotyrosine via reductive dehalogenation. To learn more about IYDs throughout biology, Phatarphekar *et al.* searched for new enzymes using a unique lid structure along with several active site residues as clues. Bioinformatics identified a number of sequences, from which the authors expressed and characterized seven new enzymes; in each case, k_{cat}/K_m values for the deiodination of monoiodotyrosine were within an order of magnitude of the known mouse homolog. The authors also noted that the annotations for some of the nonmammalian enzymes were incomplete or absent, presumably because other species have no obvious use for this enzyme. However, the authors postulate that the presence of IYD in honeybee and daphnia could be linked to reports that these species can obtain thyroid hormone exogenously. Jellyfish (related to the hydra and sea anemone proteins studied here) have previously been shown to initiate developmental changes in response to iodotyrosine or thyroid hormone, suggesting these enzymes may have unexpected regulatory roles. Finally, the more than 200 bacterial sequences may have roles in detoxification. The appropriate description of these enzymes offers new opportunities to understand the role of iodine in biological systems. *CG*

RIBOZYMES

Now for splicing!

Nature **503**, 229–234 (2013)

SEBASTIAN FICA



Ribozymes have often been considered vestigial catalytic RNAs from an earlier era. However, protein translation by the ribosome, one of the most highly conserved biosynthetic processes in the cell, is catalyzed by RNA. Fica *et al.* now establish that the spliceosome, the machinery that catalyzes pre-mRNA splicing, is fundamentally a metalloenzyme made of RNA. The spliceosome catalyzes removal of introns from eukaryotic pre-mRNAs in a two-step transesterification process that is mechanistically analogous to the one used by self-splicing group II introns. Previous structural and biochemical parallels between the spliceosome and the group II intron have led to the hypothesis that U6 small nuclear RNA (snRNA) may function as the metal-dependent catalytic core of the spliceosome. To identify potential metal binding sites, Fica *et al.* replaced key oxygen atoms at specific sites of the phosphate backbone of yeast U6 snRNA with sulfur atoms and looked for positions where splicing was inhibited by the substitution but could be rescued with a thiophilic metal ion such as Cd^{2+}. The analysis revealed five nucleotides that served as metal ligands in U6 snRNA, which are functionally analogous to those observed in crystal structures of group II introns. Further mechanistic investigations showed that the U6 snRNA assembles a single two-metal active site within the core of the spliceosome that catalyzes both steps of intron removal. *TLS*

NEUROGENERATION

Toward taming toxicity

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Science; doi:10.1126/science.1245321

Parkinson's disease (PD) is associated with pathological aggregation of α-synuclein (α-syn), with certain alleles, such as the autosomal dominant A53T mutation, causing prominent disease and dementia. Several models of PD exist, including a yeast model in which α-syn expression results in toxicity and an induced pluripotent stem cell (iPS)-based model derived from a patient harboring A53T. Chung *et al.* explored a finding from a previous yeast screen linking a nitrosative stress response transcriptional regulator, Fzf1, and suppression of α-syn toxicity. They now find that α-syn expression in both yeast and A53T iPS-derived cortical neurons induces protein nitration and perinuclear NO distribution and that expression of Fzf1 decreased the induced nitration in yeast. Manipulating NO levels in the neurons led to an altered unfolded protein response, a known component of PD. Tardiff *et al.* pursued a compound, NAB2, which was found by screening for the suppression of toxic levels of another neurodegenerative disease-linked protein, TDP-43. The compound could reverse several α-syn–induced phenotypes, including normalization of NO levels in A53T neurons. Using several genetic approaches, the authors determined the NAB2 target to be the E3 ligase Nedd4 and found that NAB2 could promote Nedd4-dependent processes, including vesicular traffic of specific cargo proteins and bulk endosomal transport. These results suggest that NAB2 rescues these seemingly disparate phenotypes associated with α-syn toxicity by activating the Nedd4 pathway. *MB*