Cilia signaling

It takes well-built cilia to send developmental signals on their way, show Tamara Caspary, Kathryn Anderson (Sloan-Kettering Institute, New York, NY), and Christine Larkins (Emory University, Atlanta, GA). Cilia that lack the correct internal architecture fail to transduce Hedgehog (Hh) signals correctly.

Hh signaling is particularly well-characterized in the developing nervous system. Depending on the amount of Hh activity, different types of neurons are produced. The particular type of neuron that forms is a result of the combination and amount of Hh-induced transcription factors.

Caspary et al. now show that this neuronal choice is impaired in a mouse mutant called hennin, which has stumpy cilia. In these animals, different Hh levels were unable to increase or decrease Gli2 activity, which was stuck at a constitutively low level. As a result, one particular type of neuron was preferentially produced.

It’s not the shortness of the cilia that’s to blame, however—other mutants with short cilia have normal Hh signaling—it’s the cilia’s internal structure. The hennin mice lacked a cilia protein called Arl13b, which appeared to be required for correct ciliary microtubule architecture.

Gli2 has also been found in cilia. Given the intermediate level of Gli2 activity in the mutant mouse cells, the authors suggest that correct ciliary architecture might be required for both activating and restricting Gli2 activity. Ciliary microtubules might, for instance, be needed for processing Gli2 into a highly active form and also for tethering Gli2 to prevent its action when it is not needed. JCB

Reference: Caspary, T., et al. 2007. Dev. Cell. 12:767–778.

The exosome exchange

Cells send RNA messages to each other by packing them into tiny membrane vesicles called exosomes, according to Hadi Valadi, Jan Lötvall (Göteborg University, Göteborg, Sweden), and colleagues. The study uncovers a new mechanism of genetic exchange between cells.

Exosomes form from the inward budding of vesicles into endosomes. If an endosome later fuses with the plasma membrane, its exosome packets can be released into the extracellular space. In this way, exosomes have been shown to send signals and present antigens to recipient cells. Proteins within the exosomes’ bellies and on their surfaces have been the main focus of study, but nobody had looked to see whether exosomes contained nucleic acids, explains Lötvall.

His team now finds that exosomes isolated from immune cells known as mast cells contain large amounts of RNA, including translatable mRNA. DNA, however, was not found in the packets.

Microarray analysis revealed the presence of approximately 1,300 different mRNAs within exosomes, which also contained miRNAs. Many of the exosomal RNAs were absent from the mast cell cytoplasm, suggesting that these might be ferried rapidly from the nucleus to their exosome transporters. Of the exosome-specific mRNAs, nearly one-fifth are implicated in pathways that regulate cellular development, protein synthesis, and posttranscriptional RNA modification.

Mast cells transferred exosomal RNA efficiently to other mast cells but not to T cells. Although it is not yet clear how dispatched exosomes interact with recipient cells, this preference suggests that exosomes have specific destinations as well as particular RNA contents. JCB

Reference: Valadi, H., et al. 2007. Nat. Cell Biol. doi:10.1038/ncb1596.

Peptides prompt prions

Short primary peptide structure drives the nucleation and self-perpetuation of prions, report Peter Tessier and Susan Lindquist (HHMI, Cambridge, MA). Prions self-perpetuate by binding their normal protein counterparts and inducing them to fold into the same abnormal conformation. Previous studies of a yeast prion called Sup35 identified a broad region of the protein that is responsible for initiating this self-perpetuation. Part of the region has unusually low sequence complexity, suggesting that its overall structure, rather than its particular amino acid sequence, might be responsible for prion proliferation. Indeed many protein domains that promote folding are themselves organized into complex tertiary structures.

Single amino acid substitutions of the low-complexity region, however, can increase or decrease Sup35’s prion-perpetuating ability. To see whether particular peptide elements might therefore be responsible, Tessier and Lindquist arrayed overlapping peptides from the broad suspect region of Sup35 onto glass slides. Only a very small set of overlapping peptides could bind and nucleate prions. And the longer the incubation continued, the more the Sup35 prion amyloids grew at these particular peptide spots.

Exactly how binding promotes conformational change is unclear. But whatever the mechanism, it does not appear to be unique to Sup35. Another distantly related yeast prion possessed a similarly short cluster of unrelated sequences capable of nucleating prions. Determining whether such sequences, which the authors call recognition elements, promote amyloid production in mammalian prions is the next step. JCB

Reference: Tessier, P.M., and S. Lindquist. 2007. Nature. doi:10.1038/nature05848.

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