RESEARCH HIGHLIGHTS

Asymmetry through retrograde trafficking

Stem cells can divide asymmetrically to accomplish both self-renewal and differentiation. In *Caenorhabditis elegans*, asymmetric localization of Wnt/β-catenin signalling components results in the production of two daughter cells with distinct cell fates. Kanamori and colleagues (*EMBO J.* **27,** 1647–1657; 2008) propose a mechanism by which this polarization can occur. In *ipla-1* mutants of *C. elegans*, intracellular phospholipase A1, β-catenin localization and cell fate are specifically disrupted in seam cells, which are stem cells in the lateral epithelium. In a search for mutations suppressing the *ipla-1* phenotype, the authors found genes constituting the endosome-to-Golgi retrograde transport machinery. It is known that Golgi sorting of proteins is crucial for their asymmetric distribution on the plasma membrane, and that lysosomal degradation of endocytosed proteins is important for polarity maintenance. Thus, the authors suggest that wild-type *ipla-1* inhibits retrograde transport, thereby promoting lysosomal degradation of endocytosed proteins, an alternative pathway to maintain cortical asymmetry of β-catenin. It remains to be determined what proteins are transported by the *ipla-1*-dependent pathway to regulate β-catenin localization. CKR

Non-coding RNA in Alzheimer's

Amyloid β 1–42, generated by β-secretase 1 activity, contributes to the pathology of Alzheimer's disease. The extent of β-secretase 1 regulation at the protein and RNA levels has been controversial. Recent studies have revealed that many sense transcripts have antisense partners, many of which are non-coding. Antisense expression can either increase or reduce the level of sense transcripts. Claes Wahlestedt and colleagues (*Nature Med.* **14,** 723–730; 2008) have identified an antisense transcript corresponding to the *β-secretase 1* mRNA. Its expression is elevated in brains from Alzheimer patients and in a mouse disease model. This antisense forms a duplex with the *β-secretase 1* mRNA, thereby increasing its stability. Knocking down the antisense in human cell lines and in mouse brains reduced the levels of the β-secretase 1 mRNA and protein, and thus lowered production of amyloid β 1–42. V arious stress conditions known to influence the pathology of Alzheimer's disease, and in particular, incubation of cells with amyloid β 1–42, increased the levels of the antisense transcript and of β−secretase 1, leading the authors to propose that a feed-forward mechanism regulates the production of pathogenic amyloid protein fragments. NLB

Sec61p bonds with ERAD substrate

During endoplasmic reticulum-associated degradation (ERAD), misfolded proteins are selectively removed from the ER and targeted for degradation by the 26S proteasome. Controversy still remains regarding the pore components required for retrotranslocation across the ER membrane. Potential candidates include Der1p, Doa1p and Sec61p, although evidence for the involvement of Sec61p has been circumstantial. Scott and Schekman (*J. Cell Biol.* **181,** 1095–1105; 2008) now provide direct evidence for the involvement of Sec61p during the retrotranslocation of a membrane-bound ERAD substrate. While investigating degradation of an artificial substrate, Deg:Sec62^{ProtA}, in mutant *sec61* strains of *Saccharomyces cerevisiae*, the authors saw that the cytosolic amino terminus of Deg:Sec62^{ProtA} became *N*-glycosylated by the ER-lumenal glycosylation machinery. Although this modification was not essential for retrotranslocation of the substrate, it led the authors to identify a disulphide-bonded intermediate between Sec61p and Deg:Sec62^{ProtA}. This disulphide bond was not seen with a mutant Deg:Sec62^{ProtA} that was not competent for ERAD, suggesting that Sec61p interacts with substrates during the retrotranslocation process. In light of this observation, more work will be required to determine how Sec61p coordinates with Der1p and Doa1p during retrotranslocation of ERAD substrates. AJ

β-arrestin smoothens cilial transport

Smoothened (Smo) is a seven-pass transmembrane receptor that regulates the activation of Gli transcription factors in response to Sonic hedgehog (Shh) signalling during development. It is known that this requires Smo targeting to primary cilia and a study from Kovacs *et al.* (*Science* **320,** 1777–1781; 2008) shows that it is driven by a complex between Smo and the kinesin motor Kif3A that is promoted by β-arrestins. Previously, β-arrestins have been shown to regulate the endocytosis of Smo and its signalling to Gli transcription factors. They also associate with Kif3A, the motor responsible for intraflagellar transport. Kovacs *et al.* therefore set out to test whether β-arrestins also affect the transport of Smo into cilia. They found that activated Smo forms a complex with Kif3A, which requires β-arrestin-1 and 2, and that this complex is important for both Smo translocation into cilia and for the effects of Shh on Gli-reporter activation. Whether this role for β-arrestins extends to other receptors localized in cilia remains to be seen. AS

Segregating age

Certain unicellular organisms, including budding yeast, age: asymmetric cell division generates a rejuvenated daughter bud and a mother cell that slows its rate of division and ultimately dies. At a critical size, daughters become mothers and age. Yves Barral and colleagues (*Nature* doi 10.1038/nature07212) have uncovered a barrier in the nuclear envelope that blocks translocation of nuclear pores (NPCs) into the bud, limiting segregation of age determinants, such as extrachromosomal rDNA circles (ERCs). Barrall and colleagues have determined how this asymmetry is achieved. Fluorescence loss in photobleaching (FLIP) of green fluorescent protein (GFP)-tagged markers for inner and outer nuclear membrane, NPCs and nucleoplasm showed that the inner membrane and nucleoplasm exchange freely between mother and bud, whereas the outer membrane and NPCs are compartmentalized: mothers accumulate pre-existing NPCs, whereas buds assemble them *de novo*. Septins form a membrane-associated collar at the bud neck; mutants for the septins Cdc12 or Shs1, or the bud neck protein Bud6, lose the diffusion barrier in the outer nuclear envelope, which mediates the asymmetric segregation of ERCs anchored to the NPCs. Finally, the buds of bud6 mutants reset their age less efficiently. Thus, in budding yeast mitosis, nuclear envelope dynamics control asymmetrical age segregation. Nuclear envelope breakdown occurs in mammalian mitosis, but progeria-associated lamin mutations suggest a role for the envelope in ageing. BP

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