The many facets of Smad regulation (p. 4359)

Commentary

Smads are intracellular signalling molecules activated following binding of members of the TGF-β superfamily to receptor serine/threonine kinases. Phosphorylation of R-Smads by the receptors allows them to form complexes with Co-Smad, enter the nucleus and regulate gene expression. A third class of Smad, I-Smads, plays an inhibitory role, competing with R-Smads for receptors and marking receptors for degradation. Carl-Henrik Heldin and co-workers discuss our understanding of Smad phosphorylation and nucleoplasmic shuttling, as well as the importance of oligomerization and ubiquitination in Smad regulation. Recent work has shown that phosphorylation of the R-Smad C-terminus allows it to interact with other Smads, leading to formation of homo-oligomers and subsequently Co-Smad-containing hetero-oligomers. Moreover, phosphorylation appears to induce a conformational change that exposes the R-Smad nuclear localization sequence, allowing importin β1 to bind and mediate Ran-dependent nuclear import. Once in the nucleus, Smads can stimulate gene expression directly, by binding to DNA or cooperating with transcription factors, and indirectly, by regulating other factors through ubiquitination.

Cell adhesion in Dictyostelium development (p. 4349)

Commentary

Cell-cell adhesion is essential during animal development: not only does it have an architectural role, but junctional proteins such as β-catenin also link cell adhesion to signalling pathways that regulate cell proliferation, differentiation and apoptosis. But how important is cell adhesion lower down the evolutionary ladder? Juliet Coates and Adrian Burgoyne and co-workers have assessed the effects of mutations that disrupt the thermostability of the 4-helix bundle during bilayer fusion in regulated exocytosis. The authors used a sensitive cellular approach in which an endogenous SNARE, SNAP-25, is removed by botulinum neurotoxin E (BoNT/E) and cells are transfected with BoNT/E-resistant SNAP-25 constructs. They demonstrate that the helix-bundle mutations affect neither the time course of exocytosis nor the kinetics of single exocytotic release events. Burgoyne and co-workers conclude that the lack of effect of these stability-reducing mutations indicates that formation of a highly stable SNARE complex does not in fact drive membrane fusion but instead takes place after fusion has occurred.

Membrane fusion in SNARE helix-bundle mutants (p. 4397)

Fusion of intracellular membranes is driven by interactions between highly conserved SNARE proteins in the two bilayers. Structural studies suggest that formation of a highly thermostable 4-helix bundle containing helices donated by each SNARE drives membrane fusion. The formation of such a stable structure cannot, however, be reconciled with the observed reversibility of fusion. Robert Burgoyne and co-workers have assessed the effects of mutations that disrupt the thermostability of the 4-helix bundle during bilayer fusion in regulated exocytosis. The authors used a sensitive cellular approach in which an endogenous SNARE, SNAP-25, is removed by botulinum neurotoxin E (BoNT/E) and cells are transfected with BoNT/E-resistant SNAP-25 constructs. They demonstrate that the helix-bundle mutations affect neither the time course of exocytosis nor the kinetics of single exocytotic release events. Burgoyne and co-workers conclude that the lack of effect of these stability-reducing mutations indicates that formation of a highly stable SNARE complex does not in fact drive membrane fusion but instead takes place after fusion has occurred.

Nuclear defects associated with human lamin A/C mutations (p. 4435, p. 4447 & p. 4459)

Mutations in the LMNA gene, which encodes the nuclear lamina components lamin A and lamin C, cause distinct inherited forms of muscular dystrophy, cardiomyopathy and lipodystrophy. But the nature of the nuclear abnormalities the different mutations produce and why they result in distinct tissue-restricted diseases are unclear. Three papers in this issue examine the effects of different lamin A/C mutations in cultured cells. Howard Woman and co-workers have transfected myoblasts with disease-linked lamin A/C mutants (see p. 4435); Brian Burke and co-workers have performed similar experiments in HeLa cells and LMNA-null fibroblasts (see p. 4447). Brigitte Buendia and co-workers have taken a slightly different approach: analysis of primary cultures of fibroblasts from individuals who have Dunnigan-type familial partial lypodystrophy (FPLD). The Woman group show that a subset of the lamin A/C mutations - those affecting the rod domain - generate intranuclear inclusions and significantly disrupt the endogenous lamina. The Burke group demonstrate that point mutations that cause dilated cardiomyopathy or Emery-Dreifuss muscular dystrophy modify assembly properties of lamin A and C and interfere with the organisation of endogenous lamins. Finally, Buendia and co-workers find that the R482Q and R482W lamin A/C mutations present in the lipodystrophy patients cause nuclear envelope defects, disrupt lamin arrangements and produce abnormal chromatin organization. Together these findings indicate that disease-associated LMNA mutations produce distinct defects in nuclear architecture and nuclear envelope organization. They thus represent a first step in our attempts to unravel the cellular pathophysiology of inherited lamin A/C disorders.

In the next issue of JCS

STICKY WICKET

Location, location, location! Caveman CELL SCIENCE AT GLANCE

Microtubule dynamics. R. Heald and E. Nogales

COMMENTARIES


RESEARCH ARTICLES

