RESEARCH HIGHLIGHTS

USP9x makes the junctions tight

Tight junctions (TJs), the most apical intercellular junctions in polarized epithelial cells, function as a selective diffusion barrier between individual cells and are involved in cellular proliferation and differentiation. Although the composition and organization of TJs has been extensively studied, the temporal regulation of TJ biogenesis in response to adhesion cues is still poorly understood. Luton and colleagues now report (*Embo J.* doi:10.1038/emboj.2010.46) that the exchange factor for Arf6 (EFA6) facilitates the formation of TJs and that the deubiquitylating enzyme USP9x allows EFA6 protein levels to build up during the establishment of cell polarity.

The authors knocked-down EFA6B, which catalyses Arf6 nucleotide exchange activity and is involved in actin cytoskeletal reorganization, using small interfering RNA in an epithelial cell line. They observed a delay in TJ assembly that could be rescued by overexpression of wild-type EFA6B but not by mutant proteins that were catalytically inactive or defective in actin remodelling. EFA6B transiently accumulated at cell–cell contacts shortly before TJ formation in cells that were induced to polarize. At steady state, EFA6B is constitutively polyubiquitylated and rapidly degraded, but EFA6B was found to associate with and be deubiquitylated by USP9x at nascent cell–cell contacts, thereby increasing EFA6B protein levels and promoting TJ biogenesis.

This study reveals a regulatory mechanism that finely tunes the assembly of TJs. FC

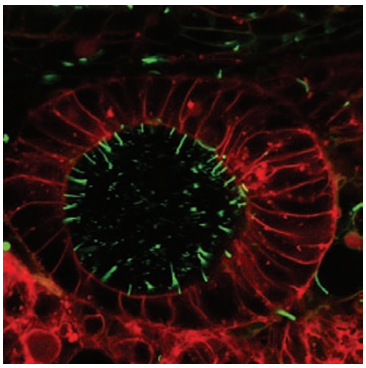
Epigenetic regulation and miRNA crosstalk.

The DNA methyl-CpG-binding protein MeCP2 controls the differentiation and proliferation of neural stem cells (NSCs), although its downstream targets are unknown, and mutations in MeCP2 are associated with neurological disorders in humans. In conjunction with the transcription factor Sox2, MeCP2 has now been found to regulate the expression of the small non-coding RNA miR-137 in mouse neural stem cells (*J. Cell Biol.* **189**, 127–141; 2010). The expression of miR-137, which normally increases during neuronal differentiation, is shown to be elevated in NSCs derived from MeCP2 knockout mice. Both MeCP2 and Sox2 bind to the promoter region of miR-137 and loss of MeCP2 correlates with loss of Sox2 binding and an increase in histone marks associated with active transcription at this regulatory region, which may account for the premature expression of miR-137 in NSCs. Overexpression of miR-137 in NSCs *in vitro* and *in vivo* promotes their proliferation and impairs their differentiation, while silencing its expression *in vitro* has the reverse effect. The authors identify the histone methyltransferase Ezh2 (Enhancer of zeste 2) as an miR-137 target, with Ezh2 expression rescuing miR-137-induced proliferation and differentiation defects. Loss of MeCP2 or miR-137 overexpression also correlate with a global decrease in histone H3-K27 trimethylation. This study highlights the intricate crosstalk between epigenetic- and miRNA-mediated regulation of gene expression during neurogenesis. NLB

Signalling? Use the Force!

Mechanical forces are known to influence tissue organisation, but how these forces are integrated with signal transduction at the level of membrane receptors is poorly understood. Jay Groves and colleagues (Science; **327**. 1380–1385; 2010) have employed the Eph receptor system to determine how physical forces influence the spatial organization and movement of ligand-receptor complexes and ligand-induced signalling. Mammary epithelial cells expressing the EphA2 receptor were cultured on a supported membrane supplied with the Eph ligand, ephrin-A1. The authors found that large ligand-receptor clusters were formed and transported towards the centre of the cell in a manner driven by actomyosin-based contractility. When physical constraints were introduced in ligand movement through membrane grid patterns, EphA2 was still activated but downstream cellular responses such as actin re-organisation, and recruitment of the protease ADAM10, were altered. Further studies are needed to determine if ephrin ligands *in vivo* are similarly controlled by tissue-mediated forces. EphA2 has been implicated in breast cancer, and the authors also quantified radial receptor movement in a panel of 26 breast cancer cell lines. Interestingly, the transport characteristics were found to correlate with invasive potential, suggesting that altered mechanical constraints may influence signalling in tumours. CKR

Rab11 promotes primary ciliogenesis



The generation of primary cilia at the cell surface depends on directional vesicular trafficking of ciliary components. The small GTPase Rab8 and its guanine nucleotide exchange factor (GEF) Rabin8 are essential for this process. Wei Guo and colleagues now show that a second Rab family member, Rab11, promotes ciliogenesis by binding to Rabin8 and activating its GEF activity towards Rab8 (*Proc. Natl Acad. Sci. USA* **107**, 6346–6351; 2010).

Similarly to Rab8, Rab11 regulates anterograde trafficking from the *trans*-Golgi network and endosomes to the plasma membrane. Guo and colleagues found that Rab11 colocalizes with Rab8 and Rabin8 at the basal body, and expression of dominant-negative Rab11 constructs, or siRNA-mediated depletion of Rab11, significantly shortens the length of primary cilia. Furthermore, *in vitro* analyses showed that Rab11 interacts with Rabin8 in a GTP-dependent manner, and that this interaction promotes nucleotide exchange on Rab8.

Bardet-Biedl syndrome (BBS) is associated with defects in primary cilia formation. Expression of a constitutively active Rab11 mutant also stimulated binding of Rabin8 to the BBS complex protein BBS1, strengthening the authors' hypothesis that Rab11 has an important role in primary cilium biogenesis. These findings also hint at the possibility that a Rab GTPase cascade regulates the generation of primary cilia. It will be important to determine if other Rab family members regulate this process. EJC

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