RESEARCH HIGHLIGHTS

A fragile link between ES and iPS cells

The capacity of human somatic cells harbouring disease-specific mutations to be reprogrammed into pluripotent cells by defined factors has raised the possibility that induced pluripotent stem (iPS) cells could replace human embryonic stem (ES) cells in basic research and clinical applications. A new study by Daley, Benvenisty and colleagues (*Cell Stem Cell* **6,** 407–411; 2010) reports important differences between ES and iPS cells in modelling the fragile X (FX) syndrome, highlighting the need for further comparative studies of ES and iPS cells.

FX syndrome, the most common form of inherited mental retardation, is caused by silencing of the fragile X mental retardation 1 (*FMR1*) gene during development. The absence of *FMR1* expression is due to the expansion of a CGG triplet repeat in the 5′ untranslated region of the gene that leads to DNA hypermethylation and repressive histone modifications. Human ES cells derived from FX blastocysts seem to recapitulate the disease-linked *FMR1* silencing — undifferentiated FX-ES cells initially express *FMR1* despite the CGG triplet repeat expansion and gene silencing occurs only on differentiation. The authors generated iPS cell lines from fibroblasts of individuals carrying the FX mutation and compared the regulation of *FMR1* transcription to that of human FX-ES cells. They found that despite successful reprogramming to pluripotent cells, the *FMR1* gene remained repressed in FX-iPS cells and carried DNA methylation and histone modifications indicative of a repressive chromatin state.

This study suggests that reprogramming may not be able to correct all epigenetic defects. FC

'Ragulating' mTORC1 activation

The mTORC1 kinase complex regulates cell growth in response to changes in nutrient availability. Increasing amino-acid levels stimulate the Rag GTPases to activate mTORC1 by facilitating its association with late endosomes or lysosomes, where it is activated by the Rheb GTPase. However, the mechanisms governing mTORC1 translocation, as well as the precise endomembrane compartment with which it interacts, have remained unclear. Sabatini and colleagues now report that a ternary protein complex, known as Ragulator, is required for mTORC1 translocation to lysosomal membranes following changes in amino-acid availability, and is a critical regulator of mTORC1 signalling (*Cell* **141,** 290–303; 2010).

Amino-acid stimulation induced mTORC1 lysosomal translocation, where it associated with lysosome-localized Rag proteins. The authors found that the Ragulator protein complex, comprising p14, p18 and MP1, interacted with the Rag GTPases. Depletion of individual Ragulator complex components blocked Rag lysosomal localization and attenuated mTORC1 translocation in response to amino acids, indicating that Ragulator recruits Rag to lysosomal membranes and hence regulates mTORC1 activation. Indeed, the Ragulator complex was required for amino-acid-induced activation of mTORC1; furthermore, forced expression of mTORC1 at lysosomal membranes rescued Rag and Ragulator deficiency, and rendered mTORC1 insensitive to changes in amino-acid levels. Thus, the Rag–Ragulator complex regulates mTORC1 activation in response to amino-acid availability by localizing mTORC1 to lysosomes. EJC

An EMAP for mechanosensing

Mechanotransduction by sensory cells allows mechanical stimuli such as sound or touch to be transmitted into a signalling response, and often occurs through a cytoskeletal mechanoreceptor structure. Howard and colleagues (*Nature Comm.* doi:10.1038/ncomms1007) have found a doublecortin-domain-containing microtubule-associated protein (DCX-EMAP) that is required for the normal structure and mechanosensing of *Drosophila* sensory cilia.

They initially characterized a set of genes that are enriched in mechanosensing campaniform receptors of *Drosophila* halteres — vestigial wing structures that are important for balance. From this set of genes, they identified DCX-EMAP as an unusual EMAP protein that lacks a coiled-coil motif, but has two doublecortin domains. In U20S cells, DCX-EMAP colocalizes with microtubules and promotes their bundling, suggesting it might have a role as a microtubule-associated protein during mechanotransduction. Indeed, flies lacking DCX-EMAP were both uncoordinated and deaf and, upon closer examination, the authors found that there were defects in both the transduction and amplification of signals in the auditory mechanosensing response. DCX-EMAP localizes to the ciliary dilation of the fly auditory Johnston's organ, and its loss appears to also disrupt its normal ultrastructure.

The authors propose that DCX-EMAP is important for microtubule-based mechanosensing, and provides a mechanistic link between transduction of mechanical signals and their amplification. AS

Cancer cell invasion: breaking down the wall

Invadopodia are specialized cell membrane protrusions that enable cancer cells to cross the basement membrane and enter the stroma. A new study published in the *Journal of Cell Biology* by Schoumacher *et al.*, (*J. Cell Biol.* **189,** 541–556; 2010) dissects the contribution of different cytoskeletal networks to invadopodia formation and elongation.

Previous work has shown that invadopodia formation depends on molecules involved in generating a branched dendritic actin network characteristic of lamellopodia, and those implicated in unbranched actin network formation. Although actin is known to be important for invadopodia formation, the roles of microtubules and intermediate filaments are unclear. Schoumacher *et al.* confirm that invadopodia contain markers specific to the dendritic actin networks of lamellipodia as well as the bundled actin structures found in filopodia. Depleting these lamellipodial and filopodial markers reduce invadopodia formation indicating that both types of actin structures are important in invadopodia. The authors found that components of both actin machineries were distributed in a manner that suggested a dendritic actin structure formed at the base of invadopodia whereas actin bundles formed the core of the protrusion. Moreover, Schoumacher *et al.* found that invadopodia contain microtubules and intermediate filaments and both microtubules and vimentin intermediate filaments are important for invadopodia elongation, but not its initial formation.

The authors propose a model wherein dendritic and bundled networks predominate during initial invadopodia formation, followed by actin bundles elongating to allow invadopodia growth, and finally, microtubules and intermediate filaments act in invadopodia elongation. SS

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