In This Issue

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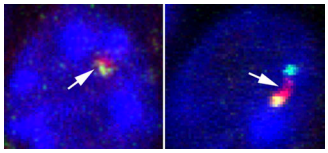
p63 delegates during skin development



The normally compact EDC cluster (arrow, left) stretches out in a cell lacking Satb1.

A molecular sibling of the cancer-fighting protein p53 orchestrates development of the epidermis by stimulating expression of a chromatin-reorganizing protein, Fessing et al. reveal.

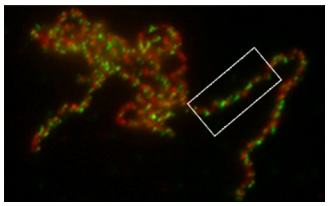
Although it doesn't receive the same attention as its more famous sibling, p63 performs an equally important job. Mice lacking the protein die shortly after birth from dehydration because the epidermis doesn't form properly. Researchers have discovered that p63 acts as a master regulator of epidermal differentiation, but whether it regulates a large number of genes directly or through intermediaries remains unclear.

Fessing et al. found that p63 has an assistant, Satb1, a protein that helps to control chromatin remodeling for the T_H2 cytokine and β-globin gene loci. Mice lacking Satb1 show an abnormally thin epidermis and reduced activity of genes that control differentiation of keratinocytes, the most abundant type of epidermal cells.

The researchers discovered that Satb1 adjusts gene activity in part by helping to arrange the epidermal differentiation complex (EDC), a cluster of more than 40 genes that manage skin development. The researchers speculate that Satb1 condenses the EDC, much as it does the T_H2 cytokine locus during T cell activation, giving the transcription machinery easy access to the genes. A question to investigate, the researchers say, is whether p63 also acts through Satb1 during differentiation of other cells, such as adult stem cells in the skin.

Fessing, M.Y., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201101148.

MCPH1 keeps chromosomes strung out



The N terminus of MCPH1 (green) and condensin II (red) occupy mutually exclusive positions on a chromosome.

A protein that's defective in patients with reduced brain size helps prevent untimely chromosome condensation, Yamashita et al. show.

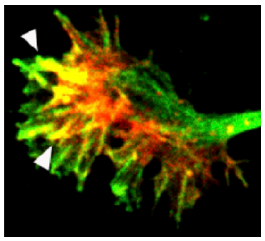
Babies born with autosomal recessive primary microcephaly have an abnormally small brain and learning difficulties. Several faulty genes can trigger this condition, including mutated versions of *MCPH1*. A clue to *MCPH1*'s function came when researchers noticed that cells from patients with defective versions of the gene undergo premature chromosome condensation (PCC), in which the chromosomes compact during G2. That observation suggested that MCPH1 mutations trigger the early activation of condensin II, a protein complex that promotes chromosome condensation during prophase.

Yamashita et al. tested that idea in *Xenopus* egg extracts. They found that human MCPH1 prevents condensin II from settling on chromosomes, a necessary step in order to initiate their condensation. In contrast, MCPH1 had no effect on two other proteins that foster chromosome condensation, condensin I and topoisomerase II. The researchers showed that the N terminus of MCPH1 blocks condensin II by competing with it for binding sites on the chromosomes. The team also determined that two mutations found in primary microcephaly patients reduce MCPH1's ability to hamper condensin II.

Those results suggest that MCPH1 regulates chromosome condensation by directly inhibiting condensin II. But how MCPH1 mutations cause microcephaly remains unclear. PCC doesn't kill cells—they can even undergo mitosis. MCPH1 and its relatives congregate on centrosomes, and the researchers speculate that the mutations weaken interactions between the centrosome and the nucleus that are necessary for the unique form of cell division that occurs during neurogenesis.

Yamashita, D., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201106141.

A kinase makes a connection



GRK5 (green) and F-actin (red) overlap (arrowheads) in the filopodia of a growing neuron.

Chen et al. identify a protein that links actin filaments to the plasma membrane in developing neurons, enabling the cells to send out new branches.

As the brain develops, neurons sprout extensions called filopodia that mature into dendrites, dendritic spines, and axons that allow the cells to communicate with other neurons. Elongation of a filopodium requires changes to the plasma membrane and to the actin cytoskeleton. For example, actin filaments polymerize and bunch up, forming bundles. Researchers aren't sure how the cell coordinates the membrane and actin renovations.

The surprising answer, Chen et al. suggest, is that a kinase does the job. The researchers discovered that the kinase GRK5 promotes filopodia formation, dendrite branching, and spine maturation. The C terminus of the protein latches onto actin filaments and spurs them to form bundles. The N terminus of GRK5 connects to the membrane phospholipid PI(4,5)P2. Preventing this interaction cuts the number of filopodia a cell can produce, Chen et al. showed. The researchers also determined that GRK5 is crucial for neural growth in vivo. Mice lacking the protein perform poorly on memory and learning tests, suggesting that their neurons aren't linking up properly.

Chen et al. hypothesize that GRK5 transmits changes in actin structure to an area of the membrane rich in PI(4,5)P2, which bulges in response, initiating a filopodium. However, GRK5 can perform its task even if it lacks its kinase activity, suggesting it is serving as a bridge between actin and the plasma membrane rather than triggering its effects enzymatically.

Chen, Y., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201104114.