In This Issue

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Three speeds of gene repositioning

Yeast use at least three different strategies to regulate how transcription factors position genes within the nucleus, Randise-Hinchliff et al. reveal.

In budding yeast, many genes are recruited to nuclear pore complexes when they are induced, potentially hastening the export of transcribed mRNAs into the cytoplasm. Repositioning can be mediated by transcription factors that bind to specific sites—called DNA zip codes—within the genes' promoters. How cells regulate gene positioning remains unknown, however.

The transcription factor Put3 binds to a zip code in the promoter of *INO1* and moves this gene to the nuclear periphery when it is induced in response to inositol starvation. Randise-Hinchliff et al. found that, in the presence of inositol, transcriptional repressors prevent Put3 from binding to *INO1*'s zip code by recruiting the histone deacetylase Rpd3(L), which presumably alters the promoter's chromatin structure.

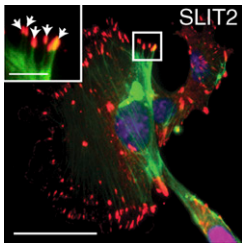
In contrast, the transcription factor Ste12 binds constitutively to the promoter of *PRM1*, and yet, the researchers found, it only moves this gene to the nuclear periphery in the presence of mating pheromone. The pheromone induces a MAP kinase signaling cascade that results in the phosphorylation and dissociation of a Ste12 inhibitor called Dig2, allowing *PRM1* repositioning.

Finally, Randise-Hinchliff et al. found that the transcription factor Gcn4 increases *HIS4* targeting to the nuclear periphery when its abundance—and thus its occupancy of the HIS4 promoter—increases in response to amino acid starvation.

Senior author Jason Brickner says that the different regulatory strategies allow cells to control gene positioning over different time scales; chromatin alterations and *INO1* repositioning are relatively slow, whereas MAP kinase signaling and *PRM1* targeting occur much faster. Changes in Gcn4 abundance, on the other hand, can fine-tune *HIS4*'s nuclear position over intermediate time scales.

Randise-Hinchliff, C., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201508068

ROBO-cop protects cells from stiff environment



The ROBO1 ligand SLIT2 induces breast epithelial cells to form large focal adhesions (red). F-actin and DNA are labeled green and blue, respectively.

Le et al. identify a signaling circuit that may protect breast epithelial cells from the tumorigenic effects of stiff extracellular matrices.

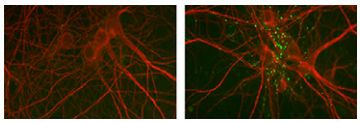
Changes in the extracellular matrix can stiffen tissues and activate oncogenic signaling pathways, but cells may try to protect themselves by remodeling their cytoskeleton and cell–matrix adhesions. ROBO receptors and their extracellular SLIT ligands—best known for their role in axonal guidance—regulate Rho family GTPases and the actin cytoskeleton, and may therefore help cells sense and respond to such changes in their environment.

Le et al. examined the ROBO signaling pathway in breast epithelial cells and found that ROBO1 and its ligand SLIT2 enhance cellular contractility by activating the Rac GTPase and stimulating assembly of cell–matrix adhesions. Stiffer environments caused breast cells to down-regulate a microRNA, *miR-203*, that normally suppresses *Robo1*, thereby elevating ROBO1 protein levels. This, in turn, enhanced cellular contractility and adhesion, allowing cells to retain their shape and position within stiff extracellular matrices.

Breast cancer cells lacking *Robo1* were more invasive, suggesting that the up-regulation of ROBO1 in stiff environments may prevent cells from metastasizing. Moreover, ROBO1 has previously been shown to suppress cell proliferation, suggesting that this pathway could delay tumor progression. Accordingly, breast cancer patients whose tumors displayed low *miR-203*/high *Robo1* expression had better long-term survival rates. Senior author Lindsay Hinck now wants to confirm that ROBO1 can counteract the protumorigenic effects of tissue stiffening in both mice and humans.

Le, L.T.-N., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201507054

Decrypting a collagen's role in schizophrenia



Cortical neurons (red) form few inhibitory synapses (green) in the absence of collagen XIX (left), but synaptogenesis is restored by a signaling peptide derived from the protein's C terminus (right).

Su et al. describe how a proteolytic fragment of collagen XIX may protect the brain from schizophrenia by promoting the formation of inhibitory synapses.

The collagen family of extracellular matrix proteins performs numerous functions in the brain, and mutations in several family members cause neurological diseases in humans. Deletion of the gene encoding collagen XIX, for example, may cause familial schizophrenia, though how this unconventional, nonfibrillar collagen promotes normal brain function is unknown.

Su et al. examined collagen XIX–deficient mice and found that they displayed a number of schizophrenia-related symptoms, including an abnormal startle response and an increased susceptibility to seizures. Schizophrenia has previously been linked to defects in a particular type of interneuron that dampens neuronal activity in the brain's cortex by forming inhibitory synapses with the cell bodies of other neurons. These inhibitory synapses were lost in collagen XIX–deficient mice although, surprisingly, wild-type animals mainly express collagen XIX in other types of cortical interneuron, suggesting that the protein promotes synaptogenesis via a paracrine mechanism.

Like other unconventional collagens, collagen XIX can be cleaved by extracellular proteases to generate a small, C-terminal signaling peptide called a matricryptin. Su et al. found that this peptide was sufficient to rescue the formation of inhibitory synapses in neuronal cultures prepared from collagen XIX–deficient mice, apparently by binding and activating the integrin adhesion receptor $\alpha_5\beta_1$.

Senior author Michael Fox now wants to learn more about how collagen XIX's matricryptin fragment promotes synaptogenesis, and to investigate whether the peptide holds any therapeutic potential for schizophrenia patients.

Su, J., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201509085