In This Issue

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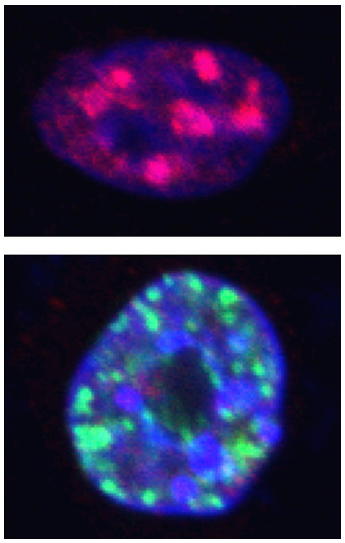
Sall4 won't give stem cells a break



DNA damage spurs Sall4 (red) to move from heterochromatin (top) to double-strand DNA breaks (green, bottom). DNA is labeled blue.

A protein that helps embryonic stem cells (ESCs) retain their identity also induces the cells to repair DNA damage, Xiong et al. report.

Fixing broken DNA is particularly important for ESCs because they pass on any mutations to their differentiated descendants. Mouse ESCs are adept at making repairs—they carry far fewer mutations than do differentiated cells—but how they achieve this isn't clear. Previous studies have revealed that double-strand breaks (DSBs) trigger epigenetic changes to ESC chromatin. Xiong et al. tested whether the protein Sall4, which suppresses differentiation of ESCs and interacts with chromatin-remodeling protein complexes, has a role in DNA repair.

The researchers found that ESCs lacking Sall4 were poor at mending DSBs. Sall4 relocated to the sites of these breaks and activated ATM, a kinase that signals DNA damage and instigates repair. Sall4 associated with Rad50, a component of the MRN complex that recruits ATM to the damage sites and turns the kinase on. The findings suggest that Sall4 either draws the MRN complex to DSBs or stabilizes the complex at these locations, thus allowing it to activate ATM.

Xiong et al. determined that Baf60a recruits Sall4 to DSBs. Baf60a is a component of the SWI/SNF complex that reorganizes chromatin at sites of DNA damage. The study raises the possibility that Sall4 performs the same role in cancer cells as it does in ESCs. Tumor cells often overexpress the protein, suggesting that it might help them fix DNA damage and survive chemotherapy.

Xiong, J., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201408106.

Desmoplakin's tail gets the message

Cells control the junction protein desmoplakin by methylating and phosphorylating its tail, Albrecht et al. show.

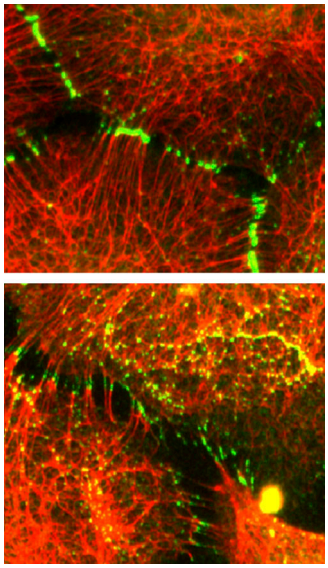
Desmosomes are heavy-duty junctions that link cells in tissues that undergo severe strain, such as in the heart and skin. Desmoplakin is a key component of the desmosome, since it anchors the intermediate filaments of the cytoskeleton to sites of cell–cell contact. Albrecht et al. determined how phosphorylation and methylation of desmoplakin's tail affect the protein's interaction with the cytoskeleton.

The kinase GSK3 phosphorylated six serines on desmoplakin's tail, and its loss spurred the protein to shift from desmosomes to the intermediate filaments. Blocking GSK3 slowed desmoplakin's relocation from the intermediate filaments to the cells' boundaries during desmosome assembly.

Methylation of four arginine residues in desmoplakin's tail had similar effects as phosphorylation. The team also found that methylation of one particular arginine, R2834, which is mutated in patients with arrhythmogenic cardiomyopathy, was necessary for phosphorylation of most tail serine residues because this alteration drew GSK3 to desmoplakin. Mutating this arginine weakened intercellular connections, causing cell layers to break apart when under mechanical stress.

The results show that phosphorylation and methylation make desmoplakin more dynamic. Cells might be able to fine-tune desmoplakin's characteristics by adding and removing phosphates and methyl groups. Thus, they could direct the protein to cell boundaries when desmosomes are forming and curtail its movement when the junctions are complete.

Albrecht, L.V., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201406020.



Desmoplakin (green) normally resides at cell–cell junctions (top), but in cells that can't methylate its tail (bottom), it gathers along intermediate filaments (red).