In This Issue

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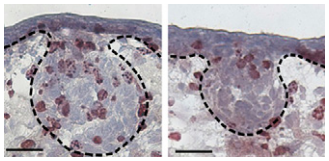
Pygo2 opens chromatin and cycles cells



Without Pygo2 (right) mammary glands have fewer cycling progenitor cells (brown).

By spreading an active chromatin state, Pygo2 prompts the proliferation of mammary gland progenitor cells, report Gu et al.

The fly version of Pygo2, Pygopus, is essential for Wg signaling. But the relationship between mammalian Wg (Wnt) and Pygo2 is less clear. Pygo2 is necessary for the development of a number of tissues, but in the two best studied—eye and testis—it has no need for Wnt.

Gu et al. looked at the relationship between Wnt and Pygo2 in mammary gland epithelial cells, where both proteins have been linked with cancer.

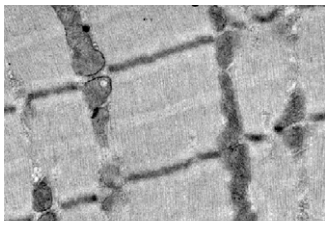
Pygo2 was expressed in mammary progenitor cells in the embryo and adult mouse, where it seemed to specifically regulate proliferation. Mammary epithelial cells that lacked Pygo2 still generated mature cell types, despite progenitor cell numbers being reduced.

Is Pygo2's proliferative power driven by Wnt? It seems so. The team found that in mice that lacked Pygo2 in mammary epithelial cells, β-catenin (the cellular effector of Wnt) could no longer induce aberrant proliferation. Wnt target genes were also down-regulated and this correlated with a reduction of histone H3 lysine 4 (H3K4) trimethylation—an epigenetic modification associated with active chromatin. Pygo2 recruited H3K4 methyltransferases, showed the team, and also bound to di- and trimethylated H3K4 suggesting it works in a positive feedback loop to spread the active chromatin mark. This activity was necessary for Pygo2-driven proliferation.

Pygo2's chromatin activity wasn't limited to Wnt targets, however. Pygo2 also associated with histone methyltransferase in bulk chromatin. This suggests Pygo2 is regulated by other pathways, and might explain its Wnt independence in certain tissues.

Gu, B., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200810133.

Heart saves muscle



Muscle cell architecture looks normal in transgenic mice that lack ACTA1 but express human ACTC.

A heart muscle protein can replace its missing skeletal muscle counterpart to give mice with myopathy a long and active life, show Nowak et al.

The contraction machinery protein, actin, exists in different forms in the adult heart and skeletal muscles. The heart form, ACTC, is also the dominant form in skeletal muscle of the fetus. But during development, the skeletal form, ACTA1, increases in production and by birth has taken over. It is not clear why the switch occurs, or why it doesn't occur in the heart, but it happens in every higher vertebrate and, for that reason, has been considered vitally important.

Mutations to the *ACTA1* gene cause a rare but serious myopathy. Most patients die within the first year of life and some are born almost completely paralyzed. Mice lacking ACTA1 die nine days after birth.

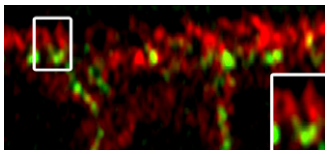
Nowak et al. wondered if ACTC could compensate for a lack of ACTA1. The two proteins differ only slightly but, like the developmental switch in production, this difference is conserved across species. Many researchers therefore assumed such compensation would never work.

But it did. Nowak and colleagues crossed *Acta1* mutant mice with transgenic mice that express human ACTC at high levels in skeletal muscle cells. The resulting mice didn't die at nine days. In fact, almost all of them (93.5%) survived more than three months, and some more than two years. The mice's locomotor performance was comparable with wild-type, as was their overall muscle strength (though individual muscle fibers were slightly weaker), and their endurance was actually higher—they ran faster and for longer.

This begs the question, Why do we even have ACTA1? Besides pondering that, Nowak and colleagues are also working out how to boost endogenous ACTC as a possible therapy for ACTA1-lacking patients.

Nowak, K.J., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200812132.

Dynamics of staying put



Cadherin clusters (green) form between microvilli (inset) before teaming up with Bazooka clusters at lateral membranes.

Without cell–cell connections our bodies would fall apart. McGill et al. have now delved into the dynamics of connection construction.

The connections are called adherens junctions. Within each cell these junctions are built, not by assembling proteins at single sites, but by bringing two different protein complexes together, the team now shows. One of the complexes, Bazooka clusters, remains steadfast at the cell cortex and catches the other complex, the cadherin–catenin clusters, as they flow along in the membrane.

To determine these dynamics, the team followed fluorescently tagged versions of the complexes in fly embryos at a stage called cellularization—when one giant multinucleated cell becomes an epithelial layer of mononucleated cells.

Bazooka clusters formed at the contacts between these cells. Meanwhile, cadherin–catenin clusters first formed between microvilli structures on the apical surface. They then moved down to the cell–cell contacts, where the Bazooka clusters were waiting.

In between microvilli might seem like a strange place to form complexes involved in cell–cell contact, but senior author Tony Harris suggests that the movement of the microvilli membranes might help accumulate the cadherin and catenin into clusters. Also, at the transition region between apical and lateral (cell–cell contact) membranes, microvilli can interlock. This could then produce clusters between neighboring cells enabling the cells to grab hold of each other.

McGill, M.A., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200812146.