The finding that Hho1 functions to inhibit recombination is surprising, as HR is an essential mechanism that is used by cells to repair DNA damage. But inappropriate activation of HR can also be extremely harmful, leading to chromosomal rearrangements that cause genomic instability — and the role of Hho1 could be to suppress this.

A second potential function of Hho1 might be to prevent cells from carrying out telomerase-independent telomere maintenance. If linker histones from higher eukaryotes are found to have similar functions, this will have important implications for tumorigenesis, which is linked in many cases to genome instability and requires the maintenance of telomere length for immortalization. So, far from being purely structural proteins, H1 histones might have important roles in cellular processes that are vital for maintaining genome integrity.

Louisa Flintoft, Nature Publishing Group

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WEB SITE

Jessica Down's laboratory: http://www.bioc.cam.ac.uk/UTOs/Downs.html

Pax7 expression — in CD45$^+$–Sca-1$^+$ cells co-cultured with a stable cell line expressing recombinant Wnt. This confirmed that Wnt signalling activates myogenic determination.

To determine how relevant Wnt signalling is *in vivo*, Rudnicki and colleagues injected the Wnt antagonists soluble-Frizzled-related proteins (sFRPs) 2 and 3 into regenerating mouse muscle. sFRP2 and sFRP3 inhibited the increase in CD45$^+$–Sca-1$^+$ cells, and the induction of Myf5, that was seen in regenerating cells following injury.

So, the authors propose that CD45$^+$–Sca-1$^+$ cells represent a main source of progenitor cells — thought to be stable and resident in muscles (rather than marrow-derived) — that have an important role in muscle regeneration. The molecular mechanisms by which they respond to Wnt signals to induce myogenesis aren't clear, and investigation of the transcriptional targets of Wnts in stem cells will be necessary. But "…the ability of injected sFRP proteins to attenuate the myogenic differentiation of CD45$^+$ stem cells unequivocally underscores the clinical potential for modulating Wnt signalling in muscle tissue".

Katrin Bussell

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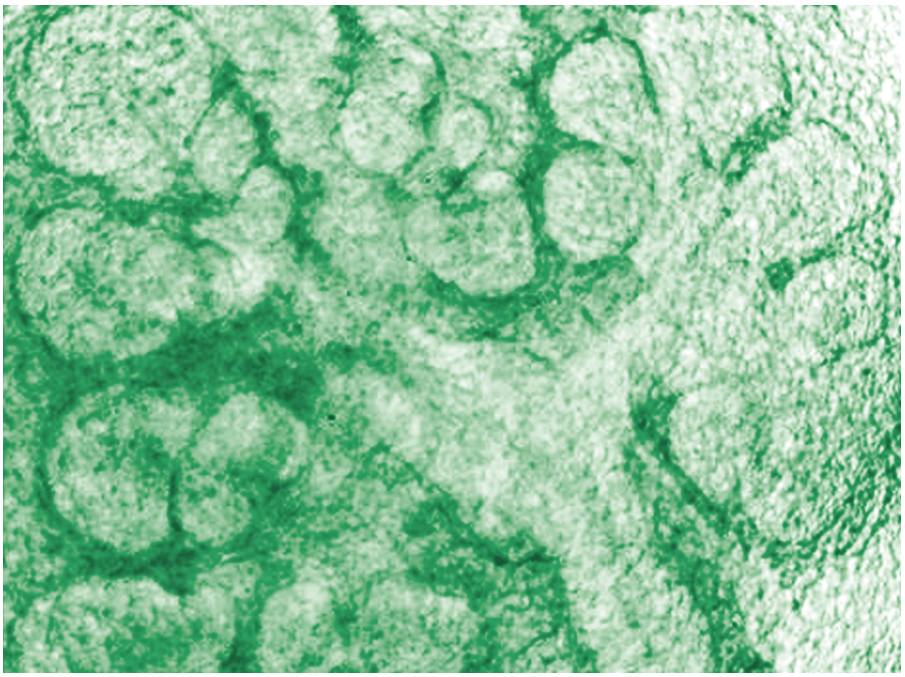

EXTRACELLULAR MATRIX

A new branch

One of the wonders of development is the process of branching morphogenesis. Characteristic of many organs such as salivary glands and kidney, complex three-dimensional epithelial branching structures arise from repetitive cleft and bud formation, but the exact mechanisms behind this are not clear. Ken Yamada's group, though, now reports on the essential role of the extracellular matrix (ECM) protein fibronectin in epithelial branching.

ECM components are already known to be required for salivary gland branching, but the authors were interested in identifying locally synthesized regulatory proteins that might influence branching. Because collagen type III accumulates at clefts and fibronectin can regulate collagen III formation, Yamada's group proposed that local fibronectin production might be important in branching morphogenesis, so they searched for differences in fibronectin messenger RNA expression in salivary glands. Quantitative reverse-transcription polymerase chain reaction showed that fibronectin mRNA was expressed at 16-fold higher levels in cleft epithelial cells than in bud epithelium. A closer look showed that cells next to nascent clefts expressed fibronectin mRNA, and high levels of fibronectin fibrils were seen in clefts of branching epithelium. Furthermore, an even closer look showed that the levels of the cell–cell adhesion molecule E-cadherin were lower in the regions right next to the fibronectin fibrils.

So if the accumulation of fibronectin fibrils promoted cleft formation during branching morphogenesis, could inhibiting fibronectin function block branching? Anti-fibronectin antibodies did indeed prevent salivary cleft formation and branching in a dose-dependent manner. Furthermore, antibodies against β_1, α_5 or α_6 integrins inhibited salivary branching. $\alpha_5\beta_1$ is a key fibronectin receptor, but the fact that combining antibodies against α_5 and α_6 more effectively inhibited branching indicated that fibronectin together with laminin ($\alpha_6\beta_1$ is its main receptor in this tissue) might be necessary for branching.

Similar to the results seen when protein function was inhibited, small interfering RNA (siRNA)-mediated knock-down of fibronectin expression in salivary-gland organ culture also markedly decreased cleft formation. Yamada's group then looked at the effects of using exogenous fibronectin to replace the fibronectin. Not only did it successfully restore branching in siRNA-treated salivary glands, but it also stimulated branching in control, non-siRNA-treated cultures in a dose-dependent manner — cleft formation was accelerated and clefts deepened. Similar observations were made in other organs — fibronectin accumulated at sites of indentation, blocking fibronectin function inhibited branching, and exogenous fibronectin promoted branching.

The authors then returned to their previous observation that cadherin levels decreased near presumptive cleft regions, and tested whether fibronectin might induce this decrease. Treating cultured salivary gland epithelial cells with fibrillar fibronectin induced local cell–matrix adhesions, but next to these sites, cadherin localization was suppressed. The predicted resultant loss of cell–cell adhesion would then provide a way for deep clefts to form. And, as well as being responsible for creating the clefts, fibronectin might also maintain them through its ability to regulate collagen, which is thought to be essential for stabilizing clefts.

Katrin Bussell

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