HIGHLIGHTS

WEB WATCH

Wnt wonderland

Wnt proteins — mediators of cell-cell signalling — are in the news again (see the Highlight on page 488) so what better place to expand your knowledge than to visit the Wnt homepage, launched and run by Roel Nusse?

The homepage itself is well presented, beginning with a short paragraph introducing the Wnt proteins. This is positioned above an overview of the contents, which is further subdivided into colour-coded sections covering different components of the Wnt signalling pathway — Wnts, Frizzled, axin and dishevelled, to name a handful. Within each section you can find information on species alignments, links to PubMed and clearly tabulated information about expression patterns, chromosomal location. For those seeking structural satisfaction, regions of axin, dishevelled and β -catenin can be viewed in three dimensions using the Cn3D program (easily obtainable from NCBI by following the links). Another resource to be particularly commended is the 'Wnt reagents and assays' section, which provides invaluable information about sources of Wnt antibodies and proteins. Included in this section are strategies for generating antisera and advice on how best to make bioactive Wnt proteins.

As no signalling molecule homepage would be complete without a signalling cascade, it is reassuring to see thumbnails on the homepage, each of which offers the option of an attractive full-size diagram. Click on one of the proteins and you instantly receive a deluge of information — perhaps even slightly visually overwhelming. Overall, the site provides extremely relevant links, including upcoming meetings (which are admirably up-to-date), reviews on Wnts and contact details of fellow Wnt workers.

Katrin Bussell

DEVELOPMENT

Hair today, gone tomorrow

Understanding how hair follicles are formed and maintained has always been a challenge, but recent findings might help get to the root of this. Reporting in *Cell*, Huelsken *et al.* have found that β -catenin has a dual role in hair follicle formation — first it mediates the formation of hair placodes (the first indication of the site of the future hair) during embryogenesis, and second it acts in the differentiation of adult skin cells.

After observing an increase in β -catenin messenger RNA expression in the epithelial part of developing hair placodes, the authors studied the function of β -catenin in skin and hair development in more detail using *Cre/lox* technology to create a conditional mutant in which β -catenin expression could be specifically deleted from the skin. Although the resultant mutant mice were viable, patches of hairless skin were seen in eight-day-old mice. Over the next two weeks, the rest of the hair grew normally, but was then lost.

Closer inspection revealed the presence of extended regions of β -catenin-negative epithelium that lacked hair placodes in 15-day-old mutant mouse embryos, in contrast to wild-type embryos, in which developing hair placodes expressed high levels of β -catenin. This implicates β -catenin in the formation of epithelial placodes. During the active phase of the hair cycle (anagen) in wild-type mice, both hair follicle and epidermal keratinocytes express β -catenin. In the conditional-mutant mice, however, both the upper part of hair follicles and the epidermis were devoid of β -catenin. During the catagen (regression and shortening) and telogen (rest) phases of the hair cycle in the mutant mice, hair was subsequently lost, hair canals widened and small cysts appeared. No new hair follicles formed, and the cysts grew and became

surrounded by a multilayered epithelium. It therefore seems that cells from the hair-follicle-derived cysts have lost their follicular characteristics and show epidermal differentiation, implying that β -catenin is needed to induce follicular differentiation.

One population of stem cells in the skin is known to give rise to keratinocyte precursors of the hair follicle and epidermis. So how does β -catenin influence the differentiation of these stem cells? And does it do this as a signalling or an adhesion molecule? In early embryos of β -catenin-deficient mice, plakoglobin (γ -catenin) is thought to compensate for the adhesive function of β -catenin. Plakoglobin, however, although present in the mutant mice, isn't thought to compensate for β -catenin signalling in the skin.

Moreover, β -catenin deficiency had no effect on the expression of tabby and downless — a ligand-receptor system that is crucial for early placode formation — but expression of bone morphogenetic protein 2 (*bmp2*), *bmp4* and *bmp7* and sonic hedgehog (*shh*) was lost in the conditional mutants. β -catenin can therefore be placed genetically downstream of tabby/downless in epithelial placode formation, but upstream of *bmp* and *shh*. It is unclear whether β -catenin targets *bmp* and *shh* directly or indirectly, and one of the next challenges will be to understand how β -catenin signalling is coordinated with other pathways involved in stem-cell differentiation.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Huelsken, J. *et al.* β -catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. *Cell* **104**, 533–545 (2001)

FURTHER READING Oshima, H. *et al.* Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell* **105**, 233–245 (2001)

TELOMERES

Mismatch repair comes to an end

Cancer cells can maintain their telomeres by reactivating telomerase or using a poorly characterized telomerase-independent mechanism. Aylin Rizki and Vicki Lundblad now report in *Nature* that a familiar cause of cancer — lack of mismatch repair — may contribute to this second mechanism.

One function of mismatch repair is to prevent recombination between imperfectly homologous sequences. As telomeres contain imperfect repeats, the authors suspected that

mismatch repair might inhibit recombination between telomeres. So, they compared the growth rates of budding yeast lacking *EST2* (*est2-Δ*) — which encodes the protein component of telomerase — with mutants lacking both *EST2* and a mismatch repair gene, *MSH2*. As expected, after about 100 generations the growth rate of the *est2-Δ* mutants was severely impaired, but in the double mutants this phenotype was less pronounced. Mutations of other mismatch repair

genes also conferred a growth advantage in an *est2-Δ* background, but the effect was reversed by deletion of *RAD52*, a gene shown previously to promote a recombination-dependent pathway for telomere maintenance. Could the growth advantage simply be a secondary consequence of mutations caused by defective DNA repair? This is unlikely because introduction of a DNA polymerase mutation that generates mutations at a similar rate to mismatch repair mutants didn't provide a growth advantage.

Are these results relevant to cancer? The authors introduced two different missense mutations into