Skin stem cells

Nicole Johnston, nicolejohnston@yahoo.com

Using stem cells obtained from skin is the therapeutic holy grail being sought for treatment of baldness and numerous skin diseases. Elaine Fuchs and colleagues at the Rockefeller University in New York, USA (http://www.rockefeller.edu), now show that stem cells grown in the laboratory from a single cell can be grafted to the back of a hairless mouse, producing a little tuft of fur, as well as new skin and functioning sebaceous glands [1].

What constitutes 'stemness'?

The novelty of their findings involved taking adult keratinocytes and confirming their 'stemness' (the ability to propagate and differentiate) using the grafting technique, effectively demonstrating that the cells from this stem cell niche were multipotent, explains William Lowry, a postdoctoral fellow and joint first author of the paper with colleague Cedric Blanpain.,' says Lowry. 'It was always somewhat assumed but was based on conjecture. The unique thing was that we were able to show it at the clonal level.'

Using microarray gene expression, they also showed that these stem cells expressed more than 50 genes known to be expressed by other types of stem cells, including blood, embryonic and neural stem cells, suggesting that the expressed genes are responsible for their 'stemness'.

Lineage mapping cell fates

Furthermore, the group's findings are the first to follow the fate of these cells *in vivo*. 'Up to now, there has been no way to lineage map the fate of a stem cell in the body,' says Angela Christiano, a researcher at Columbia University (New York, USA; http://www.columbia.edu), who wrote the accompanying

commentary in the same issue of *Cell* [2]. 'This method provides *in vivo* lineage tracing in the hair follicle – a hugely valuable technical advance.'

Using stem cells as well as cells that had already begun to differentiate into the hair follicle/shaft, Fuch's group showed that both sets of cells could give rise to new skin and hair follicles, explains Christiano. 'The cells had the potential to change their mind and revert to being more stem-like, thereby giving rise to the epidermis, hair follicle and sebaceous gland,' she says. 'The surprise was that, when grafted back on nude mice, both populations gave rise to new skin and hair follicles. They also showed that a single stem cell can give rise to everything – this is important.'

A potential treatment for hair loss

George Cotsarelis, a dermatologist and scientist at the University of Pennsylvania (Philadelphia, USA; http://www.upenn.edu), says that this could one day lead to a treatment for hair loss. 'You could generate more hair follicles than you started with, so that's really the implication here,' he says. Cotsarelis and colleagues were the first to publish the antibody technique used to isolate the stem cells [3].

In the meantime, Lowry says that they are currently studying the signalling mechanisms with that stem cell niche responsible for regulating the hair cycle. 'Understanding the signalling mechanism behind that will make it easier to understand what happening to the follicle when that's going wrong,' he says.

As for potential therapies, Christiano says that these findings provide the foundation for eventually being able to purify cells from human skin for use in gene therapy. Although it isn't known if these cells can be differentiated into other cell types, she says that both the skin and hair follicle are an accessible source of adult stem cells and is the obvious choice to pursue these possibilities.

References

1 Blanpain C. *et al.* (2004). Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell* 118, 635–648
2 Christiano, A.M. (2004). Epithelial stem cells: stepping out of their niche. *Cell* 118, 530–532
3 Trempus, C.S. *et al.* (2003) Enrichment for living murine keratinocytes from the hair follicle bulge with the cell surface marker CD34. *J. Invest. Dermatol.* 120, 501–511

Hitting the target in medulloblastoma therapy

Jane Bradbury, janeb@sciscribe.u-net.com

Researchers report that a small-molecule inhibitor of the Sonic Hedgehog (Shh) pathway can eradicate medulloblastomas in a mouse model of this brain malignancy [1]. HhAntag691, a benzimidazole derivative that blocks

  PII: S1359-6446(04)03271-4

Smoothened (SMOH) function, is an example of a class of compounds that are showing promise for medulloblastoma treatment, says Tom Curran, Chair of Developmental Neurobiology at St Jude's Children's Research Hospital, Memphis (http://www.stjude.org), 'but as this work was done in mice, we have to be cautious about assuming that this approach will work in people.'

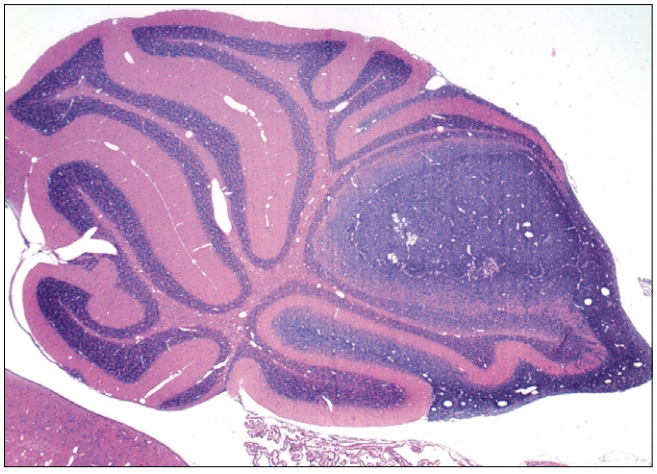
Medulloblastoma and the Shh pathway

Medulloblastoma is the commonest childhood brain tumour [2]. Current treatment relies on tumour resection followed by radiotherapy if the tumour is restricted to the brain and radiotherapy plus aggressive chemotherapy if the disease has spread. Although the five-year survival rate for medulloblastoma is about 70%, this tumour is one of the leading causes of childhood cancer deaths and those patients who survive have long-term problems, including cognitive and intellectual deficits.

Medulloblastomas arise from the precursors of the internal granule cells of the cerebellum. Shh drives the proliferation of these precursors during brain development by binding to its receptor Patched-1 (PTCH1). This derepresses the transmembrane receptor SMOH, which causes increased expression of the transcription factor GLI1 and cell proliferation. Normally, the Shh pathway is downregulated after early postnatal brain development, but *PTCH1* mutations have been detected in 10% of human medulloblastomas and, says Curran, about 30% of medulloblastomas express high levels of GLI1, making the Shh pathway a good candidate for a targeted therapy that should avoid the toxic effects of current therapies.

Shh antagonist development

Because disruption of the Shh pathway is also implicated in other tumours – basal cell carcinomas often have activating *PTCH1* mutations and hedgehog ligands are overexpressed in several tumour types – the therapeutic drug development company Curis (Cambridge, MA, USA; http://www.curis.com) began to search for a Shh antagonist about five years ago [3]. Curis, explains Chief Scientific Officer Lee Rubin, has since identified several families of antagonists. Cur61414 (now called G-024856), for example, is in late preclinical development in collaboration with Genentech (http://www.gene.com) for topical use in basal cell carcinoma. HhAntag691 is a representative of class of compounds, continues Rubin, 'that we are developing with Genentech for systemic use in solid tumours.' Curis also has licensed use patents for cyclopamine, a natural product inhibitor of Shh signalling, but, says Rubin, 'it is not currently our lead molecule because our other antagonists seem to be better.'



HhAntag691 and medulloblastoma

To test HhAntag691's potential for medulloblastoma therapy, Curran and colleagues used *Ptc1*$^{+/-}$*p53*$^{-/-}$ mice, which die from medulloblastoma within 12 weeks of birth. When the researchers treated the mice orally with 20 mg/kg of HhAntag691 twice daily for two weeks, tumour volume was reduced. 'With two doses of 100mg/kg per day, we couldn't find any indication of tumours cells being present,' notes Curran [1].

'This sort of approach to medulloblastoma treatment has great potential,' says Herbert Newton, Professor of Neurology and Co-Director of the Dardinger Neuro-Oncology Center at the Ohio State University Medical Center (http://www.osu.edu). 'Our traditional treatments are very crude and we really need to focus on tumour biology in order to improve survival for our patients. The animal model used by Curran and colleagues is a good representation of what we see in human patients but before this approach can be tried clinically, we will need to know more about how it compares with existing therapies.'

And, adds Curran, the development of Shh antagonists and other targeted therapies might require a change in how clinical trials are done. 'If we take the usual approach and treat everyone who comes along with a Shh antagonist, we may get disappointing results. We will need to choose subsets of patients who have evidence of Shh pathway disruption for inclusion in trials. If we don't, then a potentially efficacious targeted therapy may be lost.'

References

1 Romer, J.T. *et al.* (2004) Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in *Ptc1*$^{+/-}$*p53*$^{-/-}$ mice. *Cancer Cell* 6, 229–240

2 Gilbertson, R.J. (2004) Medulloblastoma: signalling a change in treatment. *Lancet Oncol.* 5, 209–218

3 Williams, J.A. *et al.* (2003) Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions. *Proc. Natl Acad. Sci. U. S. A.* 100, 4616–4621