

Draft – Embargoed until Sunday, 13 September 2009, 18:00 BST

How stem cells make skin

EMBL scientists come a step closer to understanding skin, breast and other cancers

Monterotondo, 13 September 2009 – Stem cells have a unique ability: when they divide, they can either give rise to more stem cells, or to a variety of specialised cell types. In both mice and humans, a layer of cells at the base of the skin contains stem cells that can develop into the specialised cells in the layers above. Scientists at the European Molecular Biology Laboratory (EMBL) in Monterotondo, in collaboration with colleagues at the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT) in Madrid, have discovered two proteins that control when and how these stem cells switch to being skin cells. The findings, published online today in *Nature Cell Biology*, shed light on the basic mechanisms involved not only in formation of skin, but also on skin cancer and other epithelial cancers.

At some point in their lives, the stem cells at the base of the skin stop proliferating and start differentiating into the cells that form the skin itself. To do so, they must turn off the ‘stem cell program’ in their genes and turn on the ‘skin cell program’. Researchers suspected that a family of proteins called C/EBPs might be involved in this process, as they were known to regulate it in other types of stem cell, but had so far failed to identify which C/EBP protein controlled the switch in skin. Claus Nerlov and his group at EMBL Monterotondo discovered it was not one protein, but two: C/EBP α and C/EBP β .

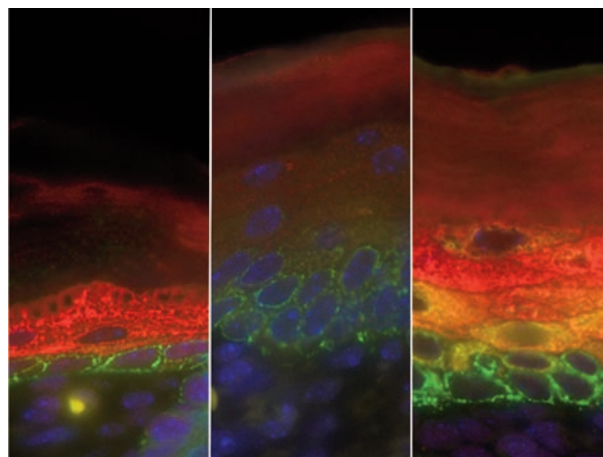
The EMBL researchers used genetic engineering techniques to delete the genes that encode C/EBP α and β specifically in the skin of mouse embryos, and found that without these proteins the skin of the mice did not form properly.

“Mice with neither C/EBP α nor β had taut and shiny skin that couldn’t keep the water inside their bodies”, Nerlov explains, “they lacked many of the proteins that make skin mechanically strong and water tight, and they died of de-hydration shortly after birth”.

However, a single working copy of either the gene for C/EBP α or the gene for C/EBP β was enough to ensure that skin developed properly. This means that the two proteins normally do the same job in the skin’s stem cells – an unexpected redundancy, which may have arisen because there are so many stem cells in skin that a tight control on proliferation is needed to avoid problems like cancer. Or it may simply be a by-product of the fact that these two proteins have different functions in other situations, such as wound healing or repair of sunlight-induced skin damage.

Source Article

Lopez, R. G., Garcia-Silva, S., Moore, S. J., Bereshchenko, O., Martinez-Cruz, A. B., Ermakova, O., Kurz, E., Paramio, J. M. & Nerlov, C. C/EBP α and - β couple interfollicular keratinocyte proliferation arrest to commitment and terminal differentiation. *Nature Cell Biology* Advanced Online Publication, 13 September 2009



In normal skin (left), the stem cells at the base, shown in green, differentiate into skin cells, shown in red. In mice whose skin has neither C/EBP α nor C/EBP β (middle), this differentiation is blocked: green-labeled stem cells appear in upper layers of skin, and there are no differentiated skin cells (no red staining). This also happens at the initial stages of basal cell carcinomas. In skin where C/EBP α is present but has lost its capacity to interact with E2F, a molecule that regulates the cell cycle (right), skin cells start differentiating abnormally, before they have properly exited the stem cell ‘program’ (yellow/orange). This is similar to what is observed in the initial stages of squamous cell carcinomas, a more aggressive and invasive skin tumour.

One of the hallmarks of epithelial cancers – which include skin, breast, and oral cancers – is that they have genes turned on which would normally only be expressed in embryonic stem cells, and which may help cancer cells divide indefinitely. Such genes become re-expressed in the skin in the absence of C/EBPs. So, by understanding how C/EBP α and β turn off such ‘stem cell’ programs, researchers hope to come a step closer to finding ways to fight such cancers.

When Nerlov and colleagues looked at how C/EBP α and - β work in the skin, they found that these proteins also regulate a number of other molecules that control skin development. Several important pathways known to control skin and hair formation were improperly activated in the mice lacking C/EBP α and - β .

“This is a very important discovery”, says Nerlov. “It opens up a lot of new areas, because we can see how these proteins control virtually every other molecule known to regulate skin cell differentiation. It seems to be a key piece in the puzzle of how our skin is formed and maintained throughout life.” ●

Contact:

Lena Raditsch, Head of Communications, EMBL Heidelberg, Germany, Tel: +49 6221 387 125, www.embl.org, lana.raditsch@embl.de

About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 20 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and associate member state Australia. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. EMBL's International PhD Programme has a student body of about 170. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome.

Policy regarding use

EMBL press and picture releases including photographs, graphics, movies and videos are copyrighted by EMBL. They may be freely reprinted and distributed for non-commercial use via print, broadcast and electronic media, provided that proper attribution to authors, photographers and designers is made. High-resolution copies of the images can be downloaded from the EMBL web site: www.embl.org