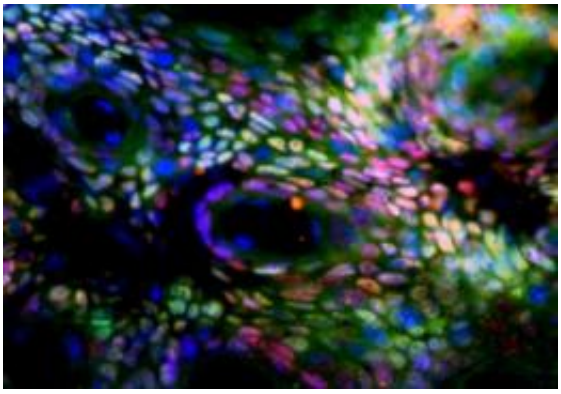
Study on skin formation suggests strategies to fight skin cancer

December 6 2010



This is a horizontal section through the basal layer of newborn mouse epidermis, stained for HDAC1 (green) and P63 (red). Nuclei are stained blue. HDAC1 and HDAC2 mediate the repressive functions of P63 in epidermal development. Credit: Matthew LeBoeuf, University of Pennsylvania School of Medicine

In a study published in the journal *Developmental Cell*, Sarah Millar PhD, professor of Dermatology and Cell & Developmental Biology at the University of Pennsylvania School of Medicine, and colleagues demonstrate that a pair of enzymes called HDACs are critical to the proper formation of mammalian skin.

The findings, Millar says, not only provide information about the molecular processes underlying skin development, they also suggest a potential anticancer strategy. "Inhibition of these HDAC enzymes might be able to shut down the growth of tumors that contain cells resembling

those in embryonic skin," she says.

Acting as a barrier to infection and dehydration, the outermost layer of the skin, called the epidermis, is a stratified structure in which progenitor stem cells in the bottommost layer continuously divide to replenish the cells in the upper layers that are lost as skin cells slough off. The origin of this structure is a single cell layer called surface ectoderm that covers vertebrate embryos.

Millar's team is interested in how surface ectoderm becomes epidermis. They decided to focus on enzymes that control gene expression by regulating the accessibility of chromatin - the DNA and protein structure in which genes reside. Within the chromatin, DNA is wound around proteins known as histones. The degree of compaction of this structure influences whether or not genes are expressed. Genes in tightly wound chromatin areas are generally inaccessible and suppressed, whereas those in "open" or loosely packed areas can be activated.

HDACs remove chemical modifications known as acetyl groups from histones, resulting in a compact and repressive chromatin environment. Previous evidence had suggested a possible role for histone acetylation in regulating epidermal development, but its exact functions were unclear.

Skin Essentials

Penn MD/PhD student Matthew LeBoeuf, the lead author of the study, deleted the genes for two HDACs in the embryonic surface ectoderm of mice, and found that in the absence of both HDAC1 and HDAC2, the epidermis fails to differentiate and the embryos die at birth. "These deacetylation enzymes, which usually act to compact the chromatin in particular regions, are absolutely essential for the skin to develop," Millar explains.

When they examined these mutant mice, Millar's team found that in addition to defective epidermis, the embryos also failed to develop hair follicles, tongue papillae, eyelids, and teeth – a constellation of defects that was reminiscent of deletion of another gene, called p63.

p63 is a transcription factor – a protein that activates or represses the expression of other genes. In this case, p63 is a kind of epidermal master regulator; its job is to ensure the formation of epidermis. When LeBoeuf examined the expression of known p63 targets, he found that those genes that are activated by p63 exhibit normal expression in HDAC mutant embryos, whereas those that are normally repressed by p63 do not. He also found that HDACs associate with regulatory sequences upstream of p63-suppressed genes, and are in fact active there; histone proteins from those regions are more heavily acetylated in keratinocytes treated with an HDAC inhibitor than in control-treated keratinocytes.

So, how does HDAC mutation lead to failure of epidermal development? As Millar explains, the genes that normally are repressed by p63 act to suppress cell division and induce cell aging. In HDAC mutants (as well as in p63 mutants), these cell division inhibitory proteins become active, stifling epidermal development by shutting down the division and self-renewal of the progenitor cell layer. "Normally, it's really important that p63 shuts down these genes," Millar says. "If it's not doing that, then the skin can't develop."

Molecular Yin and Yang

Exacerbating that problem, her team determined that HDACs also normally act to inhibit the activity of a p63-related protein called p53. p53 is the yin to p63's yang: it normally enhances the expression of proteins that suppress cell division and induce aging.

Thus, the net effect of HDAC deletion in these mice is to both prevent

repression of embryonic genes that dampen stem cell proliferation, and also to actively enhance their expression.

According to Millar, these findings suggest the possibility that HDAC inhibitors – already in clinical trials for a variety of tumors - may be useful therapeutics in the fight against certain skin cancers that are characterized by the presence of undifferentiated, embryonic-like cells. She stresses, however, that experiments on tumors were not performed in the current study. "This is more of a future direction," she says, "something our results imply."

Provided by University of Pennsylvania School of Medicine