Molecular switch controls melanin production, may allow true sunless tanning

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Discovery of a molecular switch that turns off the natural process of skin pigmentation may lead to a novel way of protecting the skin – activating the tanning process without exposure to cancer-causing UV radiation. In their report in the journal *Genes & Development*, researchers from the Massachusetts General Hospital (MGH) Cutaneous Biology Research Center (CBRC) describe how blocking the action of this switch – an enzyme called PDE-4D3 – in the skin of mice led to a significant increase in melanin production.

"The primary goal of inducing melanin production in human skin would be prevention of skin cancer, since all the common forms are known to be associated with UV exposure, " explains David Fisher, MD, PhD, director of the hospital's Department of Dermatology and an investigator at the MGH CBRC, who led the study. "Not only would increased melanin directly block UV radiation, but an alternative way to activate the tanning response could help dissuade people from sun tanning or indoor tanning, both of which are known to raise skin cancer risk."

In 2006 Fisher's group showed that the metabolic pathway leading to UV-induced pigmentation is controlled by cyclic AMP (cAMP), a molecule known to regulate many important cellular processes by carrying messages from the cell surface to internal target molecules. Using a strain of transgenic mice with red hair and melanocytes in their epidermis – common mice have none of these melanin-producing cells in the outer skin layer – they found that inducing cAMP production in the animals' skin led to significant pigmentation. But since the drug used

in that study cannot penetrate human skin, they needed to investigate an alternative approach.

Because most drugs act by blocking rather than stimulating their target molecules, better defining the pathway leading from UV exposure to melanin production could identify a step limiting melanin expression that, if suppressed, would increase production of the pigment. The strength and duration of the signals carried by cAMP are controlled by PDE enzymes, which break down the molecule after its message is delivered. Detailed analysis of the melanin expression pathway identified PDE-4D3 as the regulator of cAMP activity in melanocytes. The transcription factor activated by cAMP induces production of both melanin and PDE-4D3, and the enzyme in turn modulates the pigmentation process by breaking down cAMP.

The researchers confirmed role of PDE-4D3 in controlling melanin expression by applying several agents that block PDE production to the skin of the transgenic mice with epidermal melanocytes. After five days of treatment, the animals' skin had darkened significantly, while treament of control mice with no epidemal melanocytes produced no effect.

"Although PDE enzymes degrade cAMP within all cells, different members of this enzyme family are active in different types of cells," Fisher explains. "We showed that PDE-4D3 is particularly important within melanocytes, and while the enzyme may have a role in other cells, a blocking drug that is applied directly to the skin would probably have limited effects in other tissues." Additional research is needed to identify drugs that penetrate human skin and safely block PDE-4D3, he notes, and his team has already starting searching for such agents.

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