Study uncovers new pathways that control skin tanning and lightening

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When skin cells responsible for pigmentation are exposed to estrogen or progesterone, the cells respond by adjusting their melanin production, resulting in either skin darkening or lightening. Although pregnant women often experience alterations in skin pigmentation, the reason for the changes has long puzzled physicians. New research, from the Perelman School of Medicine at the University of Pennsylvania, has uncovered cellular pathways in skin pigment cells that are activated by estrogen and progesterone - two of the main female sex hormones - and also identified synthetic hormone derivatives that specifically influence the pigment producing pathway. Together, the findings provide critical information that could lead to the development of new products that change skin tone without exposure to UV radiation or toxic bleaching agents. The discovery is reported today in the journal *eLife*.

"Correcting disorders of human skin pigmentation is difficult, as safe and effective medications that alter melanin pigment production are lacking. But, the information uncovered in this study suggests that by using derivatives of sex hormones to selectively influence the natural melanin production machinery, we may be able to develop treatments to correct such disorders," said senior author Todd W. Ridky, MD, PhD, an assistant professor of Dermatology at the Perelman School of Medicine at the University of Pennsylvania. "Further, understanding how to manipulate skin tone without the need for harmful ultraviolet radiation or toxic chemicals could have a significant impact on the cosmetic industry, as large numbers of people around the world currently spend billions of dollars in often unsuccessful or potentially dangerous attempts

to lighten or darken their natural skin color. The development of drugs that specifically target the natural pigment production pathway in skin cells could be a safer and more effective alternative to the tanning beds and bleaching creams frequently used today."

Although the molecular signals controlling skin color are varied and complex, the observation that pregnant women often experience changes in skin tone suggested to scientists that sex hormones were likely involved. However, because there are changes in the levels of many hormones and other molecules during pregnancy, it's difficult for researchers to identify which one or which combination could be responsible for the change in pigmentation. Darkening of facial skin in pregnant women has been documented for more than 2,000 years, making this a long-standing unanswered question. But, scientists were given a clue when it was noted that women sometimes develop darker skin pigment on their face when taking birth control pills which contain only derivatives of the hormones estrogen and progesterone.

Estrogen Tans, Progesterone Lightens

In the study, human melanocytes - the cells that produce the skin pigment melanin - were exposed to estrogen levels usually seen during pregnancy. The cells responded by increasing melanin production. Ethinyl estradiol, a synthetic variant of estrogen commonly used in birth control pills, had a similar effect. Curiously, the drug tamoxifen, which usually blocks estrogen effects, also darkened skin. After four days, the melanin content of the cells increased 200 to 300 percent, which would represent a significant tanning response in skin. Melanin's light-absorbing properties allow it to block much of the UV radiation in sunlight before it damages other skin cells.

In many tissues, the effects of estrogen are counterbalanced by progesterone. Consistent with this, when melanocytes were exposed to

progesterone, melanin production decreased, causing skin to lighten.

Finding the Receptors

The results begged the question: How can estrogen and progesterone exert such effects?

In the normal sunlight-driven tanning response, UV damage triggers an increase in the production of melanocyte stimulating hormone (MSH), which is a short protein (peptide) that binds and activates another protein, the melanocortin 1 receptor (MC1R), on melanocytes. Activation of MC1R triggers a further cascade of specific signals within melanocytes, which ultimately leads to a boost in melanin production.

Researchers found that estrogen upregulates, and progesterone downregulates most of the same signaling cascade stimulated by MSH. However, it wasn't clear how the hormones were causing these effects, as neither estrogen nor progesterone act on MC1R. Further complicating the story, there was also no evidence that melanocytes express the classic estrogen and progesterone receptors (ER/PR) that are known to be responsible for much of the sex steroid effects in other tissues. The ER/PR receptors also have no known direct connection to the signaling molecules activated by MC1R.

However, further testing showed that melanocytes express a separate, non-classical, estrogen receptor, GPER, as well as a non-classical progesterone receptor, PAQR7. Neither receptor had been studied previously in melanocytes, but the results of the new study, which abolished the estrogen and progesterone effects by deleting the receptors, confirmed that the new receptors are responsible for the skin pigment effects. The Penn scientists also utilized synthetic derivatives of estrogen and progesterone that do not bind ER/PR (but still bind the nonclassical receptors) to boost skin pigment through GPER, or decrease

it through PAQR7.

As an initial step towards the development of a therapy, the researchers purified the selective GPER-activating compound, and applied it in a cream to the ears of mice. The treatment increased melanin levels by about 60 percent over three weeks, causing a noticeable darkening of the mouse skin.

Working with the laboratory of Jeffrey Winkler, PhD, the Merriam Professor of Chemistry at the University of Pennsylvania, the team now hopes to develop optimized activators - or "agonists" - of the GPER and PAQR7 receptors, for eventual testing in human clinical trials.

The team is also investigating other receptors on melanocytes that might influence melanin production. Some inflammatory conditions, for example, lead to abnormal skin darkening, and melanocytes express receptors for inflammatory signaling molecules mediators like histamine.

"We are beginning to see that melanocytes integrate signals from several receptors to modulate pigment production, which will help us build a more complete model of how pigmentation is regulated," said Christopher A. Natale, a graduate student in the Ridky Laboratory, and first author of the study.

More information: Christopher A Natale et al, Sex steroids regulate skin pigmentation through nonclassical membrane-bound receptors, *eLife* (2016). DOI: 10.7554/eLife.15104

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