Gene required for radiation-induced protective pigmentation also promotes survival of melanoma cells

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Scientists have new insight into the response of human skin to radiation and what drives the most aggressive and deadly form of skin cancer. The research, published by Cell Press in the November 21st issue of the journal *Molecular Cell*, may be useful in the design of new strategies for prevention of malignant melanoma.

The process of tanning involves synthesis of the pigment melanin by skin cells known as melanocytes. The melanin is dispersed to neighboring skin cells, known as keratinocytes, and acts as a natural sunscreen that provides some protection against the ultraviolet (UV) radiation in sunlight. UV radiation induces melanin production in melanocytes via activation of p53 in keratinocytes and subsequent activation of proopiomelanocortin/melanocyte-stimulating hormone (POMC/MSH). POMC/MSH initiates a series of signals leading to activation of genes controlling pigment production in melanocytes.

The protein encoded by paired-box homeotic gene 3 (PAX3) is essential for melanocyte development. Although recent research has implicated PAX3 in the process of pigmentation, the response of PAX3 to UV radiation in human skin is not well understood. "The network of genes that regulate PAX3 expression in melanocytes has not yet been elucidated," says senior study author, Dr. Rutao Cui from the Oncology Institute at Loyola University Chicago.

Previous work by Dr Cui and colleagues demonstrated that UV radiation inhibited transforming growth factor-beta (TGF-?? in human skin and also decreased melanin synthesis in melanocytes. "Our observations led us to examine the possibility that TGF-??might also participate in regulating the pigmentation response of skin to UV radiation. We postulated that cross-talk between keratinocytes and melanocytes may contribute to the pigmentation response of skin to UV radiation," explains Dr. Cui.

Dr. Cui's team found that TGF-?-Smad signaling inhibited PAX3 transcription in the skin and that PAX3 up-regulation in melanocytes resulted from a UV-independent loss of TGF-? in neighboring keratinocytes. Importantly, PAX3 overexpression was frequently observed in melanomas from sun-exposed skin compared with non-sun-exposed skin. The researchers went on to show that the TGF-?-PAX3 signaling pathway interacted with the p53-POMC/MSH-MC1R signaling pathway and that both were critical for pigmentation.

These results identify PAX3 as an important contributor to the UV pigmentation response and to melanoma cell survival and proliferation. "This study will provide a rich foundation for further research on skin cancer prevention by enabling us to identify targeted small molecules in the signaling pathways of the UV-induced melanogenic response that are highly likely to induce naturally protective pigmentation," concludes Dr. Cui.

Source: Cell Press