'Guardian of the Genome' Protein Found to Underlie Skin Tanning

March 8 2007

A protein known as the “master watchman of the genome” for its ability to guard against cancer-causing DNA damage has been found to provide an entirely different level of cancer protection: By prompting the skin to tan in response to ultraviolet light from the sun, it deters the development of melanoma skin cancer, the fastest-increasing form of cancer in the world.

In a study in the March 9 issue of the journal *Cell*, researchers at Dana-Farber Cancer Institute report that the protein, p53, is not only linked to skin tanning, but also may play a role in people’s seemingly universal desire to be in the sun – an activity that, by promoting tanning, can reduce one’s risk of melanoma.

“The number one risk factor for melanoma is an inability to tan; people who tan easily or have dark pigmentation are far less likely to develop the disease,” says the study’s senior author, David E. Fisher, MD, PhD, director of the Melanoma Program at Dana-Farber and a professor in pediatrics at Children's Hospital Boston. “This study suggests that p53, one of the best-known tumor-suppressor proteins in our body, has a powerful role in protecting us against sun damage in the skin.”

In a study published last year, Fisher and his colleagues found that ultraviolet (UV) radiation from the sun causes skin cells called keratinocytes to make and secrete a hormone called α-MSH, which attaches to nearby skin cells called melanocytes and spurs them to produce skin-darkening pigment called melanin. The chain of events

within keratinocytes that leads to &alph-MSH production, however, was a mystery.

Investigators knew that α-MSH is created when another protein, known as pro-opiomelanocortin (or POMC), is split apart. They also knew that the amount of POMC within cells rises sharply when they're exposed to UV rays. But they didn't know what caused the POMC to increase.

One possibility was p53. When Fisher and his colleagues examined the section of the gene for POMC that promotes production of the protein, they found it meshed nicely with p53 – suggesting that when p53 docks there, it revs up POMC production. Additional evidence came when the researchers exposed human and mouse keratinocytes to UV radiation: After six hours, levels of both POMC and p53 were far higher than normal, and the level of pigment-stimulating α-MSH was 30 times above normal.

Further experiments clinched the case for p53's role in tanning. When researchers inserted p53 into keratinocytes, POMC levels rose dramatically. When they delivered UV radiation to mice whose keratinocytes lacked p53, POMC production was not induced and the mice did not tan.

The implications of the research go beyond tanning. A common skin condition, especially among the elderly, is the development of small, dark spots that are unrelated to sun exposure. The spots arise when groups of cells begin producing pigment in response to repeated stress or irritation of the skin. Although not dangerous, the condition can be a cosmetic problem, depending on its location.

"Our research offers a potential explanation of how this condition – known as post-inflammatory hyperpigmentation, or age spots – occurs," Fisher says. "We know that it occurs as a result of stress, and p53 is a

classic ‘stress’ protein, going into action when cells experience stress-related DNA damage. What we’ve learned about p53 suggests that it may trigger the hyperpigmentation process.”

There is even the possibility that p53 protects against skin damage in a second – and previously unsuspected – way. The protein not only causes skin to tan in response to sunlight, it may also underlie people’s desire to spend time in the sun.

The same process that causes POMC to produce α-MSH also leads to the production of β-endorphin, a protein that binds to the body’s opiate receptors and may be associated with feelings of pleasure. “Even as p53 is causing skin to tan during sunlight exposure, it may also affect neuronal circuits,” Fisher says. “These proteins may provide an explicit link between the regulation of tanning and of mood. It raises the question of whether p53-mediated induction of β-endorphin is involved in sun-seeking behavior, which often increases skin cancer risk.”

Source: Dana-Farber Cancer Institute