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Redheads Carry Melanoma Risk Independent of Sun Exposure

Why are redheads more susceptible to melanoma?

People with red hair and fair skin are significantly more likely to develop melanoma than are people with darker skin. Sun exposure and ultraviolet (UV) radiation are proven risks for virtually all skin cancers, and researchers want to better understand why having red hair increases melanoma risks.

Among the deadliest cancers, melanoma can grow very aggressively and spread early if undetected. The number of cases is rising at a rate of 3 percent per year,[1] especially among fair-skinned people. Unlike other forms of skin cancer, the elevated risk in fair-skinned people is not restricted to sun-exposed skin, which raised suspicion that UV radiation may not be the only risk factor for melanoma. Working with a mouse model of the redhead phenotype, Massachusetts General Hospital researchers discovered that, surprisingly, at least part of the increased risk is unrelated to any UV exposure. Rather, the pigment responsible for red hair causes oxidative damage in the skin, and that intrinsic damage promotes melanoma formation independent of UV radiation. The study, led by David E. Fisher, MD, PhD, appeared in the November 15, 2012, issue of *Nature*.[2]

THE ROLE OF PIGMENT PRODUCTION

Pigment production is controlled by the melanocortin 1 receptor (MC1R) in melanocytes, the melanin-

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Melanoma Genesis

The laboratory of David E. Fisher, MD, PhD, genetically modified three types of mice with a BRAF mutation, the most common oncogenic mutation in melanoma. When the animals' exposure to UV radiation was blocked, researchers found:

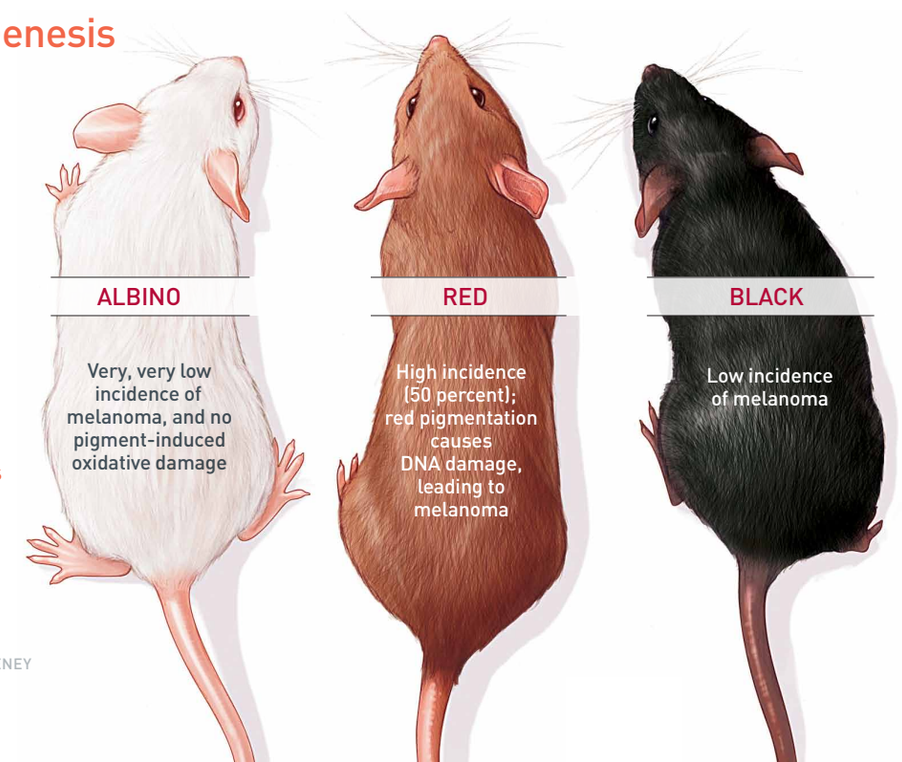

ILLUSTRATION BY DAVID CHENEY

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(continued from page 1) producing cells that become malignant in melanoma.[3] In dark-haired animals, MC1R is activated by the binding of melanocyte stimulating hormone and produces the black/brown pigment eumelanin, which shields the skin's DNA from UV waves. Redheads have an inactivated MC1R variant, causing melanocytes to produce the red/yellow pheomelanin pigment (which offers weak UV shielding), but no eumelanin.

Dr. Fisher developed a mouse model with the same inactivated MC1R variant that causes the redhead/fair-skin phenotype in humans and other animals, in order to investigate mechanisms leading to higher melanoma risks for redheads from UV radiation.

DECOUPLING UV EXPOSURE FROM INHERENT MELANOMA RISK

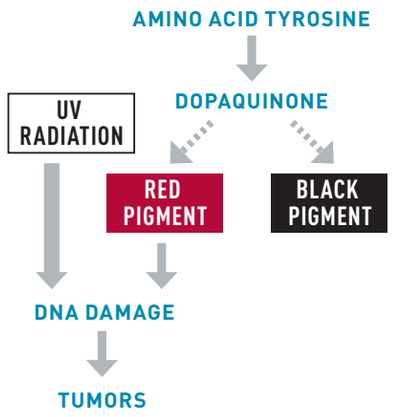
For the 2012 study, Dr. Fisher conditionally expressed $BRAF^{v600E}$, the most common melanoma oncoprotein, in the melanocytes of the redhead mice. While singular expression of this oncoprotein typically produces only benign moles, the combination of $BRAF^{v600E}$ plus the genetic red hair/fair-skin background produced a high frequency of invasive melanoma tumors without UV exposure. While it was expected that the contribution of fair skin to melanoma formation involved UV-shielding, in this case it contributed without any UV exposure. Analysis of the mouse skin cells showed that pheomelanin (red pigment) produced reactive oxygen species that damaged the DNA in the melanocytes and induced carcinogenesis.

The researchers realized that this mouse model enabled them to decouple the effect of UV radiation exposure from any UV-independent risk factor for melanoma in redheads. To explore this pigment-induced carcinogenesis, they introduced an albino allele in one group of BRAF/redhead mice, which prevented the production of any pigments, including pheomelanin. The albinos exhibited much less oxidative damage in their skin and were dramatically protected from melanoma formation in the presence of $BRAF^{v600E}$.

A third group of mice with the BRAF mutation had black hair, with a high ratio of eumelanin to pheomelanin. They had little oxidative damage and, despite the oncoprotein, a low incidence of melanoma. "Although black-haired phenotypes produce some pheomelanin, the eumelanin appears to chemically 'cage' pheomelanin, neutralizing its oxidation-damaging effect," explains Dr. Fisher.

The Pigment Pathway

Red pigment can lead to DNA damage and tumors, whereas black pigment does not; UV radiation causes damage by an unknown mechanism.



EXPLORING PREVENTIVE STRATEGIES

The current study thus establishes that the red skin pigment itself produces reactive oxygen species that damage DNA in ways that lead to melanoma in mice even without sun exposure. The therapeutic impulse might be to deploy antioxidants to counter DNA-damaging oxidants, but, Dr. Fisher cautions, some antioxidants paradoxically act as pro-oxidants. His group is rigorously exploring this question in redhead mice.

While there is a UV-independent risk for developing melanoma in redheads, Dr. Fisher emphasizes that limiting sun and UV exposure remains an important preventive strategy. First, sunscreens prevent other forms of skin cancer, and they protect against sunburns and premature aging. Second, UV radiation may exacerbate the intrinsic mutational process in redheads' melanocytes, and may be a larger contributor. Likewise, the pheomelanin-produced reactive oxygen species may contribute to the damage caused by certain UV wavelengths. The researchers are undertaking genome sequencing and biochemical studies to determine the relative contribution of environmental UV exposure and the inherent risk from red pigment.

AN AIM TO IMPROVE SUNSCREEN

This new research suggests that additional strategies are needed to prevent melanoma. Dr. Fisher and his colleagues are working to develop additional protective components for sunscreens, which may include both compounds that counter the oxidative damage inherent to redhead pigments and those that darken the melanocytes to better shield against UV light. ■

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[1] Planta, Margaret B. "Sunscreen and Melanoma: Is Our Prevention Message Correct?" *The Journal of the American Board of Family Medicine* 24, no. 6 (November 1, 2011): 735–739.

[2] Mitra, Devarati et al. "An Ultraviolet-Radiation-Independent Pathway to Melanoma Carcinogenesis in the Red Hair/Fair Skin Background." *Nature* 491, no. 7424 (November 15, 2012): 449–453.

[3] Cui, Rutao, Hans R. Widlund, Erez Feige et al. "Central Role of P53 in the Suntan Response and Pathologic Hyperpigmentation." *Cell* 128, no. 5 (March 9, 2007): 853–864.