Unexpected factor contributes to melanoma risk in red-haired, fair-skinned individuals

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The well-established elevated risk of melanoma among people with red hair and fair skin may be caused by more than just a lack of natural protection against ultraviolet (UV) radiation. In an article receiving Advance Online Publication in *Nature*, Massachusetts General Hospital (MGH) Cutaneous Biology Research Center (CBRC)and Cancer Center researchers report finding that the type of skin pigment predominantly found in red-haired, fair-skinned individuals may itself contribute to the development of melanoma.

"We've known for a long time that people with red hair and fair skin have the highest melanoma risk of any skin type. These new findings do not increase that risk but identify a new mechanism to help explain it," says David Fisher, MD, PhD, chief of the MGH Department of Dermatology, director of the CBRC and senior author of the *Nature* paper. "This may provide an opportunity to develop better sunscreens and other measures that directly address this pigmentation-associated risk while continuing to protect against UV radiation, which remains our first line of defense against melanoma and other skin cancers."

Several types of the pigment melanin are found in the skin: a dark brown or black form called eumelanin, predominant in individuals with dark hair or skin, and a lighter blond-to-red pigment called pheomelanin, the predominant pigment in individuals with red hair, freckles and fair skin. Red/blond melanin is known to be less effective than dark melanin in shielding against UV damage, but there were several hints that the incidence of melanoma in individuals of that skin type may not be fully

explained by limited UV protection. While the increased risk of non-melanoma skin cancers is limited to sun-exposed areas, the melanoma risk also applies to areas of skin not exposed to sunlight. In addition, although available sunscreens may do a good job of blocking some forms of UV damage such as sunburns, many studies have suggested that they may not be as effective protecting against melanoma as against other types of skin cancers.

In their search for additional contributors to melanoma development, the MGH team used strains of mice that were nearly identical genetically except for the gene that controls the type of melanin produced. One group of dark-colored mice had the typical variant leading to a predominance of dark melanin. Another group of mice had a "red hair-fair skin" version, the same variant that produces red hair and fair skin in humans. The researchers used a method devised by co-authors at the University of California, San Francisco and Yale University to activate the melanoma-associated form of the BRAF oncogene in patches of the animals' skin pigment cells, with the expectation that an additional environmental stress like UV radiation would be needed to induce melanoma formation. They were surprised to find that within months, half of the red mice had developed melanomas, while only a few dark mice had.

After confirming that there was no unexpected UV radiation in the area where the mice were housed, the investigators wondered whether red pigment itself might be carcinogenic. Since the red hair/fair skin gene controls many cellular activities beyond pigment production, they tested the melanoma risk within a group of red hair/fair skinned mice in which all pigment production had been genetically disabled, a strain called "albino redheads." The researchers observed that complete removal of the red-pigment pathway profoundly protected those mice from melanoma formation, indicating that something about the pigment itself, and not other aspects of being red-haired and fair-skinned, was leading

to melanoma.

Suspecting that the red-pigment-associated risk might be chemically related to the generation of reactive oxygen species (ROS) – unstable oxygen-containing molecules that can damage cells – the researchers examined skin from both red and albino redhead mice. They discovered elevated levels of a type of DNA damage typically produced by ROS in skin of red mice but not in albino redheads, supporting oxidative damage as the mechanism behind red-pigment-associated melanoma formation.

While this result suggests antioxidant treatments may be able to reduce this risk, Fisher cautions that further research is needed to identify safe and effective ways to exploit this knowledge. "Antioxidant treatments are not highly predictable in their actions and in some instances have even been seen to increase rather than prevent oxidative damage. Therefore we need to determine how to control this pathway safely and effectively," he says. "There are additional key questions to investigate, such as whether these findings also may pertain to people with, for example, fair skin and dark hair.

"Right now we're excited to have a new clue to help better understand this mystery behind melanoma, which we have always hoped could be a preventable disease," he adds. "The risk for people with this skin type has not changed, but now we know that blocking UV radiation – which continues to be essential – may not be enough. It will be important for these individuals to be aware of changes in their skin and never hesitate to have something checked by a dermatologist, even if they have scrupulously protected themselves from sun exposure, which we continue to encourage. About six out of seven melanomas will be cured if they are found early, so we need to heighten awareness and caution."

Along with Fisher, the Wigglesworth Professor of Dermatology at Harvard Medical School, co-authors of the *Nature* paper are lead author

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