Some skin cancers may start in hair follicles

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Some of the most deadly skin cancers may start in stem cells that lend color to hair, and originate in hair follicles rather than in skin layers, a new study finds.

Hair follicles are complex organs that reside within skin layers. It is there that immature pigment-making cells develop cancer-causing genetic

changes—and in a second step—are exposed to normal hair growth signals, say the study authors.

Past models of the disease had argued that sunlight (e.g., ultraviolet radiation) was a major risk factor for melanoma—but current work argues that the triggers are always there in normal follicles.

The new study, published online November 4 in *Nature Communications*, found that unlike their normal counterparts, newly cancerous pigment stem cells then migrate up and out of the follicles to establish melanomas in nearby surface skin before spreading deeper. The study was conducted in genetically engineered mice, with the results confirmed in human tissue samples.

"By confirming that oncogenic pigment cells in hair follicles are a bona fide source of melanoma, we have a better understanding of this cancer's biology and new ideas about how to counter it," says corresponding study author Mayumi Ito Suzuki, Ph.D., associate professor in the Ronald O. Perelman Department of Dermatology at NYU School of Medicine and Perlmutter Cancer Center.

Invisible Trail Revealed

The study results reflect development, in which a human starts as a single stem cell, the embryo, and becomes a fetus made up of hundreds of cell types. Along the way, stem cells divide, multiply and specialize, until, finally, they become cells capable of playing a single role (e.g., nerves, skin, etc.).

Complicating matters, stem cells can become more than one cell type, and can shift between them. This flexibility is useful during development, but can be dangerous in adults, in whom cancer cells are thought to re-acquire aspects of early embryonic cells. Because of this

malleability, researchers have theorized that melanomas might arise from several stem cell types, making them hard to treat and their origins difficult to track.

The new study addresses the stem cells that mature into melanocytes, cells that make the protein pigment melanin, which protects skin by absorbing some of the sun's ultraviolet, DNA-damaging rays. By absorbing some wavelengths of visible light, but reflecting others, pigments "create" hair color.

In a series of elegant steps, the research team established a new mouse model for the study of melanoma, one engineered such that the team could edit genes in follicular melanocyte stem cells only (the c-Kit-CreER mouse). This capability enabled researchers to introduce genetic changes that made only melanoctye stem cells—and their descendants destined to form melanomas—glow no matter where they traveled.

Able to accurately track a key stem cell type for the first time, the authors confirmed that melanoma cells can arise from melanocyte stem cells, which abnormally migrate up and out of hair follicles to enter the epidermis, the outermost layer of skin. The team then tracked the same cells as they multiplied there, and then moved deeper into the skin layer called the dermis.

Once there, the cells shed the markers and pigment that went with their follicular origins, presumably in response to local signals. They also acquired signatures similar to nerve cells (neurons) and skin cells (mesenchymal), molecular characteristics "almost exactly like" those noted in examinations of human melanoma tissue.

Knowing where to look for the original, cancer-causing event, the researchers temporarily eliminated signals one by one in the follicular environment to see if cancer still formed in their absences.

In this way, the team confirmed that follicular melanocyte stem cells, even though they had cancer-causing genetic mutations, did not multiply or migrate to cause melanomas unless also exposed to endothelin (EDN) and WNT. These signaling proteins normally cause hairs to become longer and pigment cells to multiply in follicles.

"Our mouse model is the first to demonstrate that follicular oncogenic melanocyte stem cells can establish melanomas, which promises to make it useful in identifying new diagnostics and treatments for melanoma," says first study author Qi Sun, Ph.D., a postdoctoral fellow in Ito's lab. "While our findings will require confirmation in further human testing, they argue that melanoma can arise in pigment stem cells originating both in follicles and in skin layers, such that some melanomas have multiple stem cells of origin."

Provided by NYU Langone Health

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