

# **Age-related lung changes provide pathway for metastatic growth of dormant melanoma cancer cells**

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Spreading cancer cells that escape a primary tumor site can seed in tissues distant from the tumor, but may take several years or decades to

grow into full metastatic cancers. Understanding of tumor dormancy, the process by which this happens, was incomplete. Now, new laboratory research directed by investigators at the Johns Hopkins Kimmel Cancer Center and the Johns Hopkins Bloomberg School of Public Health finds that secreted age-induced changes in distant sites such as the lung can effectively reactivate dormant cells and cause them to grow.

The researchers found that age-related changes in the secreted factors from the lung fibroblasts, normal noncancer [cells](#) in the vicinity of the tumor, facilitated a pathway for growth of dormant melanoma cells. Age-related changes in the skin microenvironment suppressed the growth of melanoma cells but drove their dissemination, seeding the deadly spread of cancer to distant organs. The results of this multicenter study were published in the June 1 issue of *Nature*.

Aging can play a role in the development of cancer metastases, says senior study author Ashani Weeraratna, Ph.D., the E.V. McCollum Professor and chair of the Department of Biochemistry and Molecular Biology at the Bloomberg School of Public Health, a Bloomberg Distinguished Professor (cancer biology), a professor of oncology and co-leader of the cancer invasion and metastasis program at the Kimmel Cancer Center.

The study found that when melanoma cells were injected into the skin of young (8 weeks old, equivalent to young adult human) and older mice (18 months old, equivalent to humans age 55 to 65), they traveled to the lungs at similar rates initially, but in the aged lung, they grew rapidly and formed bigger tumors, whereas in the younger lung, they tended to remain as small, single-cell or double-cell colonies.

The researchers grew melanoma cells together with human skin or lung fibroblasts—common cells that help maintain the structure of tissue and repair injury—from young (under age 35) or older (above age 55)

healthy donors. Melanoma cells in the aged lung fibroblast environment dramatically increased in proliferation compared to those in a young lung fibroblast environment. Conversely, melanoma cells in an aged skin fibroblast microenvironment proliferated more slowly when compared with young skin fibroblasts. Laboratory studies of melanoma cells suggested that changes in factors secreted by the fibroblasts were key to promoting these differences.

Next, the study team performed proteomic analysis (a study of proteins) on factors secreted by healthy human young and aged lung fibroblasts. The team identified changes in the WNT signaling pathway, specifically in secreted frizzled related proteins (SFRPs) that regulated WNT5A, a protein involved in various processes including melanoma metastasis. The researchers found WNT5A to be a master regulator in activating melanoma cell dormancy in the lung, enabling efficient dissemination, seeding and survival of melanoma cells in metastatic niches, but suppressing their outgrowth.

"These changes were very consistent with a phenomenon in melanoma we call phenotype switching, in which melanoma exists either in a state of growing or invading," Weeraratna says. "What our data showed is that these cells use different arms of the WNT pathway to switch back and forth between these two states," she adds. "When the WNT5A signaling pathway is activated, the cells are highly invasive but not very proliferative and don't grow fast. By contrast, when the WNT5A signaling pathway is suppressed, the cells grow much faster."

Age-induced re-programming of the lung fibroblasts increases the secretion of the protein sFRP1, which inhibits WNT5A and enables metastatic outgrowth. The team also identified the tyrosine kinase receptors AXL and MER—which play a role in normal cell proliferation—as helpers promoting the process from dormancy to reactivation.

"Our data revealed an unexpected complexity in the role of WNT signaling and other downstream pathways in melanoma cell dormancy and metastasis initiation that is regulated by aging," says lead study author Mitchell Fane, Ph.D., a postdoctoral fellow in Weeraratna's laboratory. "WNT5A promotes the initial dissemination of the tumor cells but then acts to maintain them in a dormant state to allow survival and adaptation in the lungs. This state is maintained until age-related changes in the distal site induce an emergence from tumor dormancy. Then, sFRP1 is secreted at higher levels by aged [lung fibroblasts](#) and decreases WNT5A expression to allow the reactivation from dormancy in the aged [lung](#). We also defined an axis where AXL-MER converge downstream of WNT5A that helps reactivate the dormant cells."

Much research is still needed to better understand the microenvironment at distant sites, including the brain, where [melanoma](#) also can metastasize, says Weeraratna.

**More information:** Ashani Weeraratna, Stromal changes in the aged lung induce an emergence from melanoma dormancy, *Nature* (2022).

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