Aging impacts therapeutic response of melanoma cells

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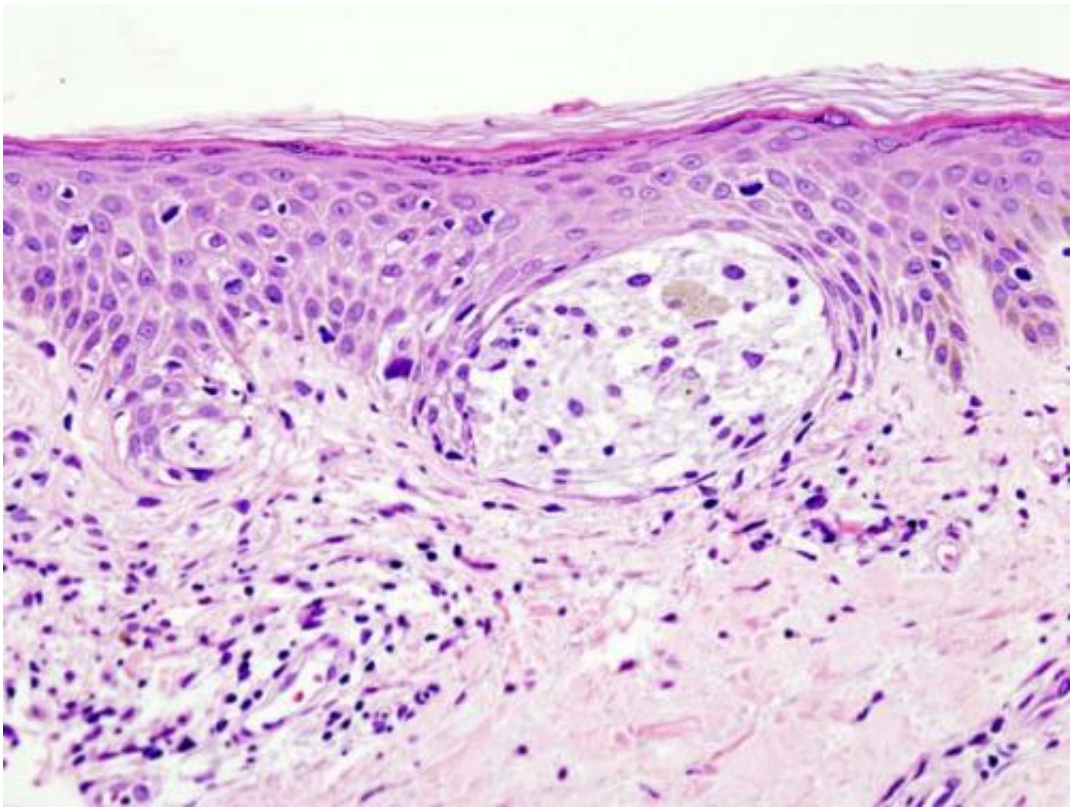

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Cancer risk increases with one's age as accumulated damage to our cells and chronic inflammation occur over time. Now, an international team of scientists led by The Wistar Institute have shown that aged tumor cells in melanoma behave differently than younger tumor cells, according to

study results published in the journal *Nature*.

Changes in the microenvironment make these older tumor cells more metastatic and more resistant to treatment with targeted therapies. In light of these findings, the scientists demonstrated how antioxidants could serve as a better treatment strategy for older patients with melanoma.

"It's fascinating to see that the microenvironment can have such a profound effect on both metastasis, and response to a therapy that is specifically targeted to a mutation in a gene. This tells us that no tumor is an island, and even therapies targeted against these driver mutations are affected by the way the tumor cell communicates with its microenvironment," said lead author Ashani Weeraratna, Ph.D., associate professor in the Tumor Microenvironment and Metastasis Program at Wistar.

Melanoma is the deadliest form of skin cancer, and patients with advanced cases of the disease only have a 20 percent chance of surviving five years after their diagnosis. Multiple targeted therapies for melanoma have been approved in the last few years, but patients who receive these drugs eventually relapse and become resistant to these treatment options.

While multiple factors may contribute the age-related increases in cancer, for the first time, the Weeraratna Lab has pinpointed age-related changes that occur in the microenvironment of tumor cells. Cells found in the skin called dermal fibroblasts help the skin recovery from injuries, and can contribute to the growth and invasion of melanoma cells. The researchers used dermal fibroblasts from healthy donors 25-35 years of age or from donors 55-65 years of age to understand what factors contribute to the difference in melanoma progression in aging cell populations.

Weeraratna and colleagues determined that a secreted factor sFRP2 was present in aging cells. SFRP2 regulates another protein called β-catenin that normally blocks the invasion of melanoma cells. In addition, b-catenin loss has been shown to promote oxidative stress in some cell types. The researchers showed that in an aged microenvironment, there are fewer scavengers of free oxygen radicals, leading to more activity of reactive oxygen species (ROS). At the same time, the age-induced loss of beta-catenin renders melanoma cells less capable of dealing with ROS, resulting in a genetically unstable tumor.

Treatment resistance experienced by older melanoma patients was found with increased activity of ROS and decreased levels of β-catenin all contribute to increased resistance to treatment with drugs that inhibit a gene, BRAF, mutated in approximately half of all cases of melanoma. Wistar scientists also showed how antioxidants might be a more effective strategy for treating older melanoma patients. An antioxidant called N-acetylcysteine (NAC) killed melanoma cells in aged dermal fibroblasts.

"Our findings highlight how vital it is to treat that melanoma in an age-appropriate manner," said Amanpreet Kaur, a graduate student in the Weeraratna lab and first author of the study. "With other studies confirming the effectiveness of anti-oxidants in treating BRAF-mutated cancers, we have more evidence of how an older population may benefit from new therapeutic strategies."

Wistar's business development team is actively seeking meaningful collaborations with biotechnology and pharmaceutical partners to comprehensively interrogate the tumor microenvironment's response to targeted therapies.

More information: Amanpreet Kaur et al. sFRP2 in the aged microenvironment drives melanoma metastasis and therapy resistance,

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