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Anti-aging gene identified as a promising therapeutic target for older melanoma patients

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Scientists at The Wistar Institute have shown that an anti-diabetic drug can inhibit the growth of melanoma in older patients by activating an anti-aging gene that in turn inhibits a protein involved in metastatic progression and resistance to targeted therapies for the disease. The study was published online in *Clinical Cancer Research*.

Even more than other types of cancer, melanoma is a disease of aging, with older patients more frequently diagnosed with the disease and having a worse prognosis. Targeted therapies have brought benefits in terms of overall survival compared to chemotherapy but they are limited by intrinsic or acquired resistance. Wistar scientists have previously shown that age-related changes in the tumor microenvironment—or the surrounding area where tumor cells crosstalk with normal and immune cells—can drive melanoma progression and therapy resistance. They have also discovered that a protein named Wnt5A promotes metastatic progression, resistance to therapy and poorer prognosis, and one of the ways in which it is regulated is by the anti-aging protein Klotho. The new study shows that treating mice with a drug that promotes Klotho expression reduces the levels of Wnt5A and decreases the growth of therapy-resistant melanoma in aged mice but, importantly, not in young mice.

"We have already shown that age-related changes in the tumor microenvironment are accountable for the higher metastatic potential of

melanoma in older patients," said Ashani Weeraratna, Ph.D., Ira Brind Associate Professor and program leader of the Tumor Microenvironment and Metastasis Program at Wistar and lead author of the paper. "Our new study indicates that a differential therapeutic approach can be beneficial for older patients in melanoma and suggests that age should be taken into account to design better treatments for certain cohorts of patients."

Weeraratna's team used an artificial skin reconstruct model to recreate the interactions of melanoma cells with either a young or aged tumor microenvironment. They observed an intricate reciprocal regulation between Klotho, Wnt5A, melanoma cells, and the tumor microenvironment. They also showed that they could manipulate Klotho expression pharmacologically using the anti-diabetic drug rosiglitazone, which resulted in decreased levels of Wnt5A. Importantly, while using rosiglitazone in conjunction with targeted therapy reduced tumor growth in both young and aged pre-clinical models, using rosiglitazone alone accelerated tumor growth in young models, while inhibiting it in aged ones.

"We believe that there is a threshold effect whereby the levels of Klotho, dictated mostly by the age of the patients, are crucial in determining whether they will benefit from this treatment or not," said Reeti Behera, Ph.D., a postdoctoral researcher in the Weeraratna lab and first author of the study. "Previous studies had tested the use of rosiglitazone for cancer treatment, but the outcome was not encouraging. I think they may have been missing a piece of the puzzle, by not considering aging and the tumor microenvironment."

This research lays the foundation for the development of promising adjuvant therapy for older melanoma patients. More studies will be needed to confirm the benefits in human subjects. Klotho is a secreted protein that can be measured in the serum of patients and this can help in

determining which patients would benefit from rosiglitazone therapy and would be eligible for further studies.

Provided by The Wistar Institute