Age-related changes in male fibroblasts increase treatment-resistant melanoma, study finds

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Ashani Weeraratna, Ph.D. Credit: Will Kirk/JHU

Age-related changes in the fibroblasts, cells that create the skin's structure, contribute to the development of aggressive, treatment-

resistant melanoma in males, according to research in mice by the Johns Hopkins Kimmel Cancer Center.

The study appears in *Cell*.

The risk of developing melanoma, a potentially deadly skin cancer, increases with age. Men are more at risk than women, and tend to develop more aggressive, hard-to-treat melanomas, particularly at advanced ages, says Ashani Weeraratna, Ph.D., the Bloomberg Distinguished Professor, E.V. McCollum Professor, and chair of the Department of Biochemistry and Molecular Biology at Johns Hopkins. The study was co-led by Yash Chhabra, Ph.D., who is now an assistant professor at Fox Chase Cancer Center in Philadelphia.

Weeraratna and colleagues have demonstrated that age-related changes in the normal cells around tumor cells—the tumor microenvironment—contribute to cancer outcomes. So, they wanted to find out whether age- and sex-related changes might interact to contribute to sex-linked disparities in melanoma.

"Melanoma is far more aggressive in men than women," Weeraratna explains. "Do normal cells around the tumors age differently in men versus women?"

Fibroblasts make collagen, a protein that gives the skin structure and strength. In previous research, Weeraratna and colleagues showed that age-related changes in fibroblasts promote the spread of melanoma tumor cells and lead to worse outcomes. Now, they confirm that fibroblasts age differently in men and women, and the age-related changes that occur in male fibroblasts contribute to more aggressive, hard-to-treat melanomas.

When they transplanted melanoma tumor cells into aged male or female

mice, they found more DNA damage accumulated in cells transplanted in the male mice. It didn't matter whether the transplanted tumor cells had come from male or female mice.

"It's not the male or female tumor cell itself," she explains. "Age-related changes in male fibroblasts that make up the tumor microenvironment account for differences in DNA damage."

In experiments comparing aged human male and female fibroblasts, they discovered that the male fibroblasts accumulated reactive oxygen species that stress and damage cells. They also found that the aged male fibroblasts produce higher levels of bone morphogenic protein 2 (BMP2), a protein usually involved in the development of bone and cartilage.

Ramping up BMP2 production using either genetic or recombinant protein approaches causes melanoma cells to become more invasive and resistant to targeted anticancer therapies. Blocking BMP2 production using a natural inhibitor makes them more sensitive to anticancer therapies in both male and female mice.

The study has significant implications for cancer research. Currently, most preclinical cancer studies use young mice. However, Weeraratna shows that studying cancer in older mice and aging human cells is essential.

"We also need to understand whether men and women respond differently to therapies, and better tailor their therapy to both sex- and age-related differences," she says.

Weeraratna and her team are now studying how age- and sex-related changes in immune system cells surrounding melanoma cells affect how well the tumors respond to immune cell-boosting therapies increasingly

used to treat melanoma. They would also like to study age- and sex-related changes in other cancers, including pancreatic cancer.

More information: *Cell* (2024).

Provided by Johns Hopkins University School of Medicine

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