

Researchers identify a mechanism controlling tumor cell recognition by immune cells

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Melanoma. Credit: Wikimedia Commons/National Cancer Institute

Immunotherapy has become a standard treatment approach for several types of cancer, including melanoma. However, tumors can escape immune cell detection even with the use of immunotherapies. In a new study published in *Cancer Immunology Research*, Moffitt Cancer Center researchers, in collaboration with the University of Miami's Miller

School of Medicine, describe a cellular mechanism that controls tumor cell recognition by immune cells.

Agents that activate the immune system in advanced melanoma have significantly improved outcomes, and many patients have long-term responses following immunotherapy treatment. However, according to James Mulé, Ph.D., associate center director of Translational Science at Moffitt, "There remains a subset of melanoma patients treated with immune-based therapies who do not achieve clinical benefit. Understanding the mechanisms underlying both successful and failed immune responses may help improve immunotherapeutic approaches."

Moffitt researchers believe that one reason why patients may not respond well to immunotherapies is because their immune system does not recognize tumor [cells](#) properly. They hypothesized that the STING protein signaling [pathway](#) may be a contributing factor to immune cell recognition.

The STING pathway is known to contribute to the activation of the [immune system](#) by stimulating the production of protein messengers called interferons. Defects in STING signaling have been reported in several different types of cancer, including melanoma; however, the impact of these defects is unclear. In order to improve our understanding of how defects in STING signaling may contribute to cancer, the Moffitt team conducted a series of laboratory experiments in human melanoma cell lines.

The researchers discovered that there are many human melanoma cell lines that have completely lost expression of STING and do not respond to signaling that activates the pathway. They also found that some human melanoma cell lines maintain STING expression, but are still incapable of activating the signaling pathway. This suggests that an unknown alternative mechanism may also be responsible for defects in STING

signaling, other than loss of STING expression itself.

In order to determine how STING signaling functions under normal circumstances, the researchers conducted experiments in human melanoma cell lines that express a functional STING pathway. They discovered that activation of STING results in production of the molecular messengers interferon-beta and CXCL10 that stimulate inflammation and an immune response. Activation of STING also caused human melanoma cells to increase the expression level of proteins called MHC molecules on their cell surface that allow them to be recognized and targeted by [immune cells](#) called T cells. Conversely, human [melanoma](#) cells that had dysfunctional STING signaling were much less able to be recognized by T cells.

These observations suggest that one mechanism by which [tumor cells](#) bypass immune detection may be through alterations in the STING pathway. The researchers hope that their work will lead to an improved understanding of immune cell activation and better treatment approaches for patients. "Further understanding of the regulation and function of STING in melanomas and other tumor types may lead to the development of strategies that target the STING pathway to improve the efficacy of adoptive cell therapy and other immunotherapies in patients who do not currently benefit from these interventions," said Mulé.

More information: Rana Falahat et al, STING Signaling in Melanoma Cells Shapes Antigenicity and Can Promote Antitumor T-cell Activity, *Cancer Immunology Research* (2019). [DOI: 10.1158/2326-6066.CIR-19-0229](#)

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