'Suffocating' cancer: Improved melanoma immunotherapy

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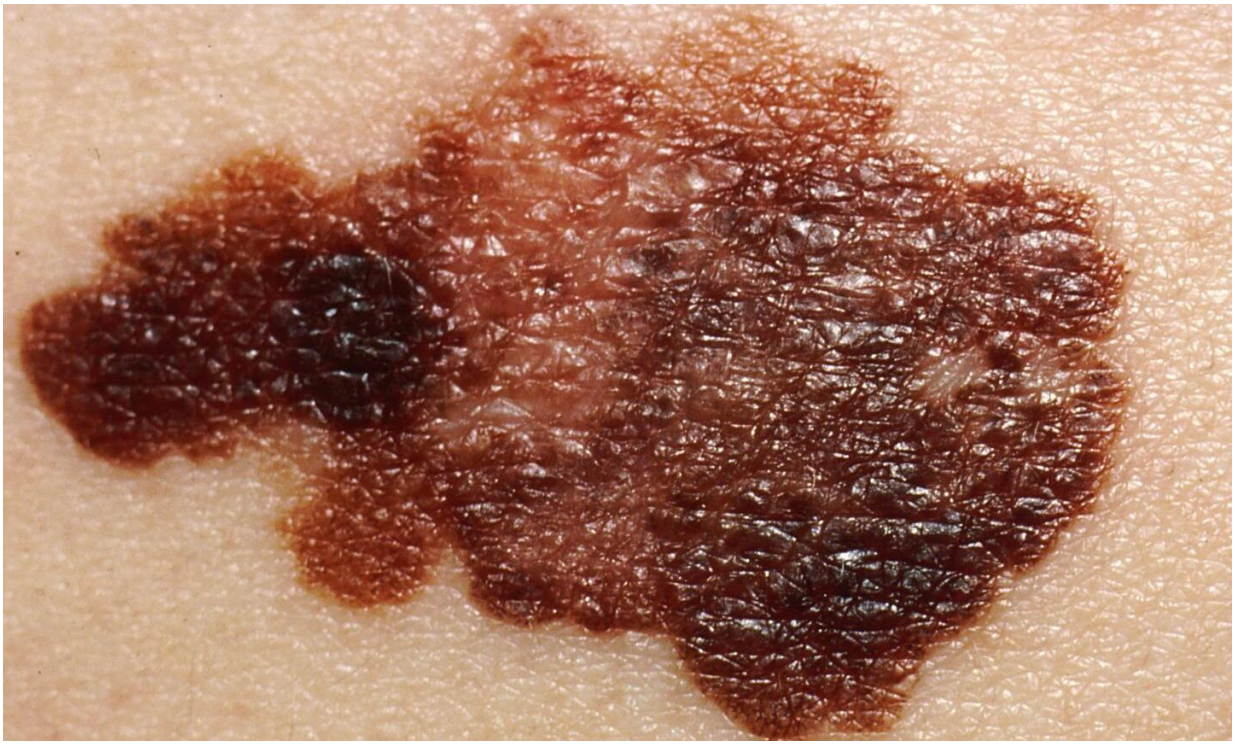

Melanoma. Credit: Wikimedia Commons/National Cancer Institute

Hypoxia, or the inadequate oxygenation of a tissue, is a condition occurring frequently in all solid tumors such as melanoma skin cancer. Melanoma cells are not only able to survive oxygen deprivation, but also to use it to their own advantage by hijacking the anti-tumor immune response and developing resistance mechanisms to conventional anti-

cancer therapies. A key gene responsible for cancer cell adaptation to hypoxia is HIF-1α (Hypoxia Inducible Factor-1 alpha).

Led by Dr. Bassam Janji, head of the Tumor Immunotherapy and Microenvironment (TIME) research group at the Luxembourg Institute of Health (LIH) and in collaboration with Gustave Roussy Cancer Center in France and the Thumbay Research Institute of Precision Medicine at Gulf Medical University in the United Arab Emirates, the team used gene editing technologies to show how targeting HIF-1α could not only inhibit tumor growth, but also drive cytotoxic (toxic to cells) immune cells to the cancer tissue. This discovery provided a valuable new target to make resistant melanomas more vulnerable to available anti-cancer treatments. Their findings were recently published in the reputable *Oncogene* Journal.

Melanoma is a type of skin cancer that develops from melanocytes, cells that are responsible for the production of pigments. Melanomas become harder to treat if not detected early, with emerging treatment resistance being an important barrier to their effective management. Due to their rapid growth rate and low blood supply, solid tumors including melanoma often exhibit areas of hypoxia. Hypoxia, or the decrease of oxygen in the tumor microenvironment, would normally cause tumor cell death.

"However, certain solid tumors have evolved to survive this hostile microenvironment by activating HIF-1α, a gene reported to be a major factor mediating the adaptive response to changes in tissue oxygen level," explains Dr. Janji. William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza were awarded the Nobel Prize in Physiology or Medicine in 2019 for their discovery of HIF-1α and how cells use it to sense hypoxia. Hypoxia has also been reported to be responsible for the failure of tumor response to conventional anti-cancer therapies and can prevent the infiltration of immune cells into the tumor. It is therefore

crucial to understand the mechanisms by which cancer cells overcome this hypoxic environment to improve the effectiveness of available anti-cancer therapies.

In this context, the team led by Dr. Janji sought to inactivate the functionality of the HIF-1α gene using CRISPR gene editing technology and investigate the impact of such inactivation on tumor growth, immune cell infiltration and response to immunotherapy in a preclinical melanoma mouse model.

"Our study revealed that blocking the activity of HIF-1α significantly inhibited melanoma growth and amplified the infiltration of immune cells into the tumor microenvironment by increasing the release of CCL5, a well-defined mediator involved in driving cytotoxic immune cells to the tumor battlefield," summarizes Dr. Audrey Lequeux, first author of the publication. Importantly, the study also showed that combining a drug devised to stop hypoxia significantly improves melanoma immunotherapy.

When the results were validated retrospectively in a cohort of 473 melanoma patients, the hypoxic signature of tumors was correlated to worsened outcomes and the lack of immune cell infiltration into tumors, which is considered as a major characteristic of tumor resistance to immunotherapies.

"Together, our data strongly argue that therapeutic strategies disrupting HIF-1α would be able to modulate the tumor microenvironment to permit the infiltration of immune cells. Such strategies could be used to improve vaccine-based and immune checkpoint blockade-based cancer immunotherapies in non-responder melanoma patients," conclude Dr. Chouaib and Dr. Janji from Gulf Medical University and Luxembourg Institute of Health, respectively.

More information: Audrey Lequeux et al, Targeting HIF-1 alpha transcriptional activity drives cytotoxic immune effector cells into melanoma and improves combination immunotherapy, *Oncogene* (2021). DOI: 10.1038/s41388-021-01846-x