How skin cancer cells sidestep the immune system

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Researchers at the Mainz University Medical Center have discovered a new signal pathway employed by skin cancer cells to avoid attack by the immune system. In an animal model and through analysis of human tissue samples, Dr. Toszka Bohn, Dr. Steffen Rapp and Professor Tobias Bopp were able to demonstrate the significant role played by a specific protein called ICER. Tumors grow less rapidly when ICER is not present. The researchers recently presented their study in *Nature Immunology*.

Over the course of evolution, the immune system has developed effective mechanisms to detect pathogens invading the body from outside and to eliminate them before they can cause major damage. However, the body is also exposed to dangers from inside. Such threats can take the form of genetic mutations from which a tumor can ultimately develop. But how do these abnormal cells elude detection by the immune system? Which immune evasion mechanisms do they use? In order to be able to develop new immunotherapy approaches in the treatment of cancer, it is first necessary to identify these mechanisms.

"In our paper in *Nature Immunology*, we report on a previously unknown immunoevasion mechanism used by the type of skin cancer known as melanoma," said Dr. Toszka Bohn, researcher at the Institute for Immunology of the Mainz University Medical Center.

Among other things, cancer cells are characterized by very rapid growth. The cells of tumors need a great deal of energy for this, which they

obtain by means of a high rate of metabolic turnover. "We were able to show that the rate of metabolic turnover in melanomas is particularly high, which results in an abnormal acidification of the tumor environment," explained Professor Tobias Bopp, co-author and spokesperson of the Research Center for Immunotherapy (FZI). Because of this acidic micromilieu, certain immune cells called macrophages that have migrated into the tumor develop into M2 macrophages, which are a specific sub-type of anti-inflammatory macrophage.

M2 macrophages are usually involved in wound healing processes and the regeneration of damaged tissue. These properties now benefit the growth of the tumor. Through a more detailed analysis of the mechanism, the researchers discovered that a protein known as inducible cAMP early repressor (ICER) is substantially involved in the process of macrophage transformation into the M2 sub-type.

"In an animal model we were further able to prove that the immune response to tumors is boosted or, in other words, the growth of cancer is slowed, if we eliminate ICER or interrupt the corresponding signal pathway," Dr. Toszka Bohn pointed out. "Comparable results obtained in analogous experiments using human tissue as samples underline the clinical relevance of our findings."

The ICER protein, which the team in Mainz is investigating, is the focus of one of 18 sub-projects of the new Collaborative Research Center (CRC) 1292 on "Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections" that was set up in January 2018. "The mechanism identified through our work provides new insight into how the immune system can be hampered when it comes to fighting cancer, thus giving us potential options for developing innovative treatment approaches," concluded Professor Hansjörg Schild, spokesperson of CRC 1292. The goal of the CRC is to build on the knowledge gained to develop new personalized immunotherapies for the

treatment of both cancers and chronic infections.

More information: Toszka Bohn et al. Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages, *Nature Immunology* (2018). DOI: 10.1038/s41590-018-0226-8