Preventing tumors from shedding their identifying proteins allows immune system to attack

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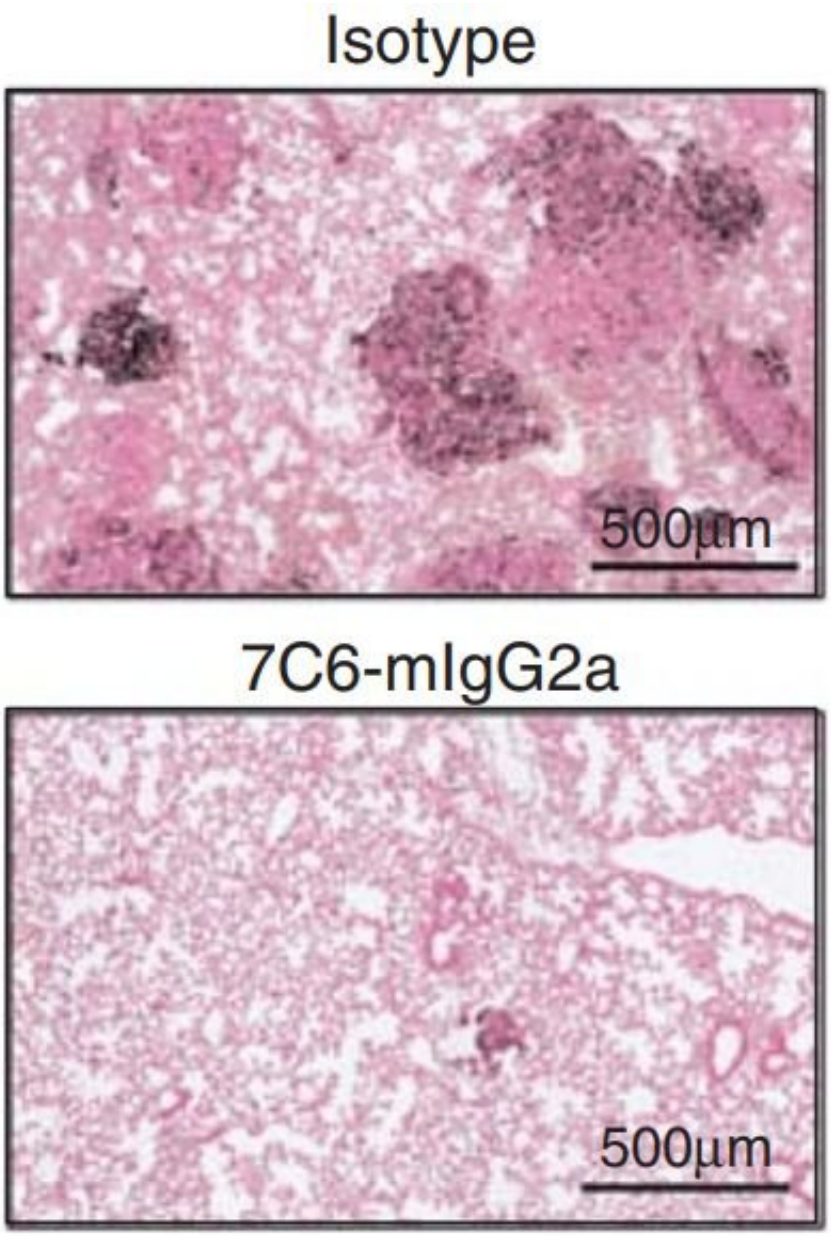

Histological analysis (Fontana-Masson staining) of lung tissue demonstrated an apparent reduction in the number and size of metastases in mice that were treated with the MICA antibody (representative of five mice). Credit: *Science* (2018). DOI: 10.1126/science.aao0505

A team of researchers with the Dana-Farber Cancer Institute and Brigham and Women's Hospital in the U.S. has found that introducing an antibody into a cancerous mouse model prevented the escape of ligands from a tumor surface allowing natural killer cells to attack. In their paper published in the journal *Science*, the group describes their technique and how well it worked. Lewis Lanier with Heidelberg University, Medical Faculty Mannheim in Germany offers an overview of the work done by the team in a Perspective piece in the same journal issue and also gives an overview of immunotherapy research in general.

Prior research has shown that one of the reasons the immune system has trouble recognizing tumors as a threat is the their tendency to shed proteins that the immune system uses to identify them. In this new effort, the researchers focused on MICA and MICB, proteins that are produced by tumors and wind up on their exposed surfaces, which the immune system would normally be able to identify. But before that can happen, the tumor actually produces an enzyme that separates the proteins from the tumor surface—essentially shedding them and preventing the immune system from using them as a signal to go on the offensive. In this new effort, the researchers looked into whether there might be a way to prevent tumors from shedding such proteins, thereby allowing the immune system to do its work.

After some searching, the team settled on an antibody called mAb 7C6—they found that when applied to mouse models with lung cancer

and melanoma, the antibody caused levels of both MICA and MICB to increase on tumor surfaces, suggesting that the tumor had been unsuccessful in shedding them. Furthermore, they also found that killer immune cells were then alerted to the tumor and attacked it, which, the researchers report, resulted in a reduced tumor load.

The technique, Lanier notes, is one of many that are being developed to help the immune system fight tumors, rather than attacking tumors directly via medical interventions. Such therapies, it is believed, will have fewer undesirable side-effects.

More information: Lucas Ferrari de Andrade et al. Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell–driven tumor immunity, *Science* (2018). DOI: 10.1126/science.aao0505

Abstract
MICA and MICB are expressed by many human cancers as a result of cellular stress, and can tag cells for elimination by cytotoxic lymphocytes through natural killer group 2D (NKG2D) receptor activation. However, tumors evade this immune recognition pathway through proteolytic shedding of MICA and MICB proteins. We rationally designed antibodies targeting the MICA α3 domain, the site of proteolytic shedding, and found that these antibodies prevented loss of cell surface MICA and MICB by human cancer cells. These antibodies inhibited tumor growth in multiple fully immunocompetent mouse models and reduced human melanoma metastases in a humanized mouse model. Antitumor immunity was mediated mainly by natural killer (NK) cells through activation of NKG2D and CD16 Fc receptors. This approach prevents the loss of important immunostimulatory ligands by human cancers and reactivates antitumor immunity.