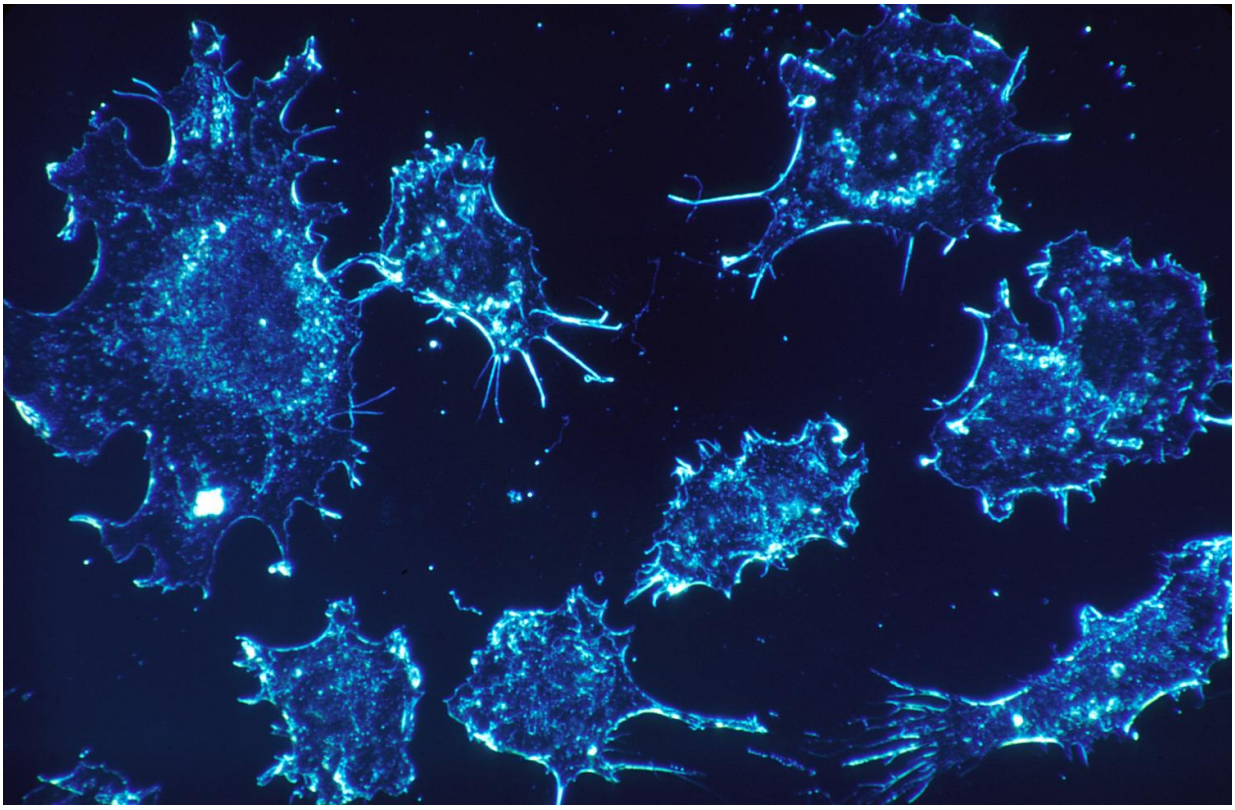
MedicalXpress

# Researchers convert pro-tumor macrophages into cancer killers

August 21 2019



Credit: CC0 Public Domain

Epithelial cancers, such as cancers of the lung and pancreas, use the αvβ3 molecule to gain drug resistance to standard cancer therapies and to become highly metastatic. In a paper published in *Cancer Research*, University of California San Diego School of Medicine researchers

identified a new therapeutic approach in mouse models that halts drug resistance and progression by using a monoclonal antibody that induces the immune system to seek and kill αvβ3-expressing cancer cells.

"This antibody is designed to seek and destroy the most stem-like, drug-resistant, aggressive tumor cells. It does this by building a bridge between tumor-associated macrophages and these highly aggressive tumor cells," said David Cheresh, Ph.D., Distinguished Professor and vice chair of Pathology. "What we have been able to observe in mice is that when we give this drug to drug-resistant tumors, it prolongs their response to standard of care and prevents their capacity to enter the blood stream."

Using the αvβ3 antibody LM609, Cheresh and his team exploited the appearance of αvβ3 receptors on tumor cells to redirect tumor-associated macrophages (TAMs) into recognizing and killing αvβ3 expressing tumor cells.

During the study period, no tumor progression or drug resistance was detected while untreated animals developed tumor growth and metastasis. The research in mouse models focused on pancreatic and lung cancer cells treated in combination with LM609 and the EGFR inhibitor erlotinib. But, the antibody is expected to work in combination with various drugs currently used to treat cancer patients, said Cheresh.

"We have observed a highly significant link between the appearance of αvβ3 expressing tumors and the appearance of tumor-associated macrophages," said Cheresh, associate director of innovation and industry alliances at UC San Diego Moores Cancer Center. "Normally, the appearance of tumor-associated macrophages promotes tumor growth and metastasis. However, our antibody arms these macrophages to join our fight against the cancer."

Macrophages are specialized immune cells that promote tissue inflammation, stimulate the immune system and rid the body of foreign debris, including cancer cells. TAMs instead create a pro-tumor environment that accelerates tumor growth, angiogenesis (the development of new blood vessels to support the tumor) and suppresses immune recognition of the tumor by the host immune response.

As tumors progress, the abundance of TAMs increases, allowing the cancer to become more aggressive and spread. As tumors become drug-resistant, αvβ3 appears on cell surfaces.

The Cheresh lab previously discovered that αvβ3 is upregulated on various cells during normal wound repair and in cancer cells as cancer becomes invasive. In both cases, this molecule triggers cells to enter a stress-tolerant state. In normal epithelial cells, this state enables them to initiate tissue remodeling, such as healing. In cancer, it allows cells to become drug-resistant and highly metastatic.

The current study revealed a new approach to induce TAMs to reverse course, killing cancer cells rather than supporting them. The antibody prompts these macrophages to begin killing tumor cells through a mechanism known as antibody-dependent cytotoxicity (ADCC).

"These results were initially unexpected since macrophages usually destroy cells via phagocytosis, a process that involves them literally devouring the foreign or target cell," said Cheresh, a faculty member of the Sanford Consortium for Regenerative Medicine. "Also, ADCC is typically known to be induced by natural killer cells, but we saw very few of these NK cells in the late-stage, drug-resistant cancers we have examined."

"We believe that the effectiveness of this antibody is based on three things: Its capacity to recognize drug-resistant cancers. Its ability to bind

to a particular receptor on tumor-associated macrophages. And its capacity to induce ADCC of these highly aggressive tumor cells."

The protein CD47, which is found on many cells in the body and is often hijacked by cancer cells, tells macrophages not to eat these cells. The αvβ3 antibody bypasses the CD47 "don't eat me signal" by inducing ADCC as opposed to phagocytosis.

"In our studies, macrophages are not killing through phagocytosis which would be blocked by the appearance of CD47 on the tumor cell target. Rather, we're inducing macrophage to kill its tumor cell target by its ability to mediate ADCC. The therapeutic antibody we are utilizing is bridging the macrophage to the αvβ3-expressing tumor cell as a target. When this occurs it releases a cytotoxic substance that kills the tumor cell."

The team is currently producing a humanized version of this antibody, which Cheresh hopes will do in humans what LM609 does in mice.

**More information:** Hiromi I. Wettersten et al. Arming tumor-associated macrophages to reverse epithelial cancer progression, *Cancer Research* (2019). DOI: 10.1158/0008-5472.CAN-19-1246

Provided by University of California - San Diego