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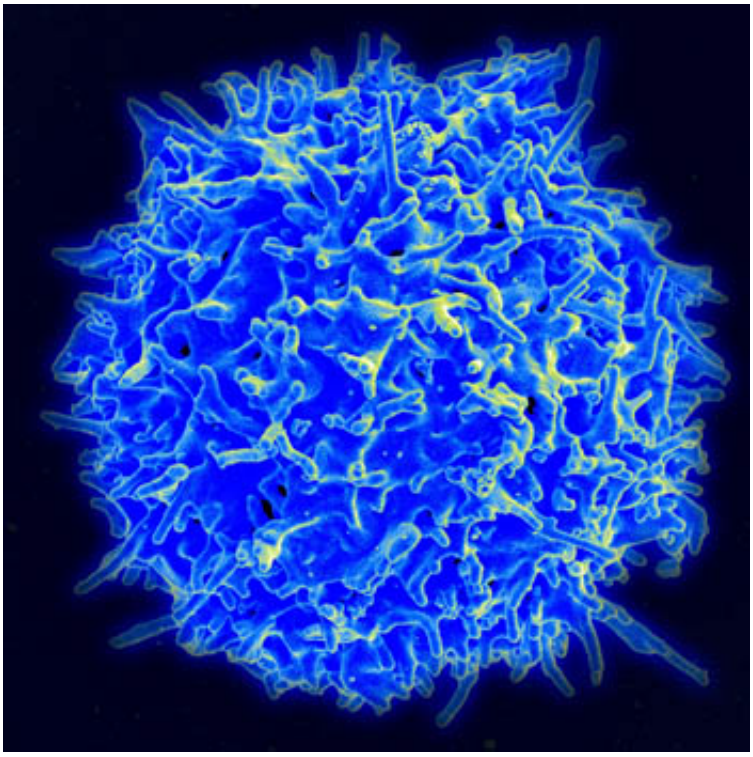
Scientists modulate cholesterol metabolism to potentiate T-cell antitumor immunity

March 16 2016



Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

As key players in the immune system, T cells provide tumor surveillance and have direct antitumor effects. However, tumors can escape T-cell attack through various mechanisms in the tumor microenvironment. Reactivating the antitumor effects of T cells has shown great clinical benefits in treating various cancers. The current T cell-based cancer

immunotherapies are, nevertheless, only effective in a limited group of patients. New cancer immunotherapies are needed, therefore, to benefit more patients.

In their new study, Prof. XU Chenqi's group and Prof. LI Boliang's group with the Institute of Biochemistry and Cell Biology (SIBCB) of the Shanghai Institutes for Biological Sciences, found that inhibiting cholesterol esterification can potentiate the antitumor activity of CD8+ T cells (also known as killer T cells).

This new way of improving T-cell function might be used as a complement to current cancer immunotherapies, such as immune checkpoint blockade.

Their research, entitled "Potentiating the antitumour response of CD8+ T cells by modulating cholesterol metabolism," was published in *Nature* on March 17.

The researchers investigated T-cell antitumor immunity from a new perspective. They believe that modulating T-cell metabolism can make killer T cells more "metabolically fit" to fight tumor cells. As a key component of membrane lipids, cholesterol is important for T-cell signaling and function.

Scientists found that inhibiting the cholesterol esterification enzyme ACAT1 can increase the plasma membrane cholesterol level and therefore promote the T-cell signaling and killing process. A small molecule inhibitor of ACAT1, avasimibe, was used to treat cancer in mouse tumor models and showed good antitumor effect. A combination of avasimibe and anti-PD-1 antibody, a checkpoint blockade drug, showed even better antitumor effect.

This study opens a new field of cancer immunotherapy and identifies

ACAT1 as a promising drug target. It is worth mentioning that avasimibe was tested in clinical trials to treat atherosclerosis and had a good human safety profile. Therefore, avasimibe could be a good drug candidate for cancer immunotherapy.

More information: *Nature*, DOI: 10.1038/nature17412