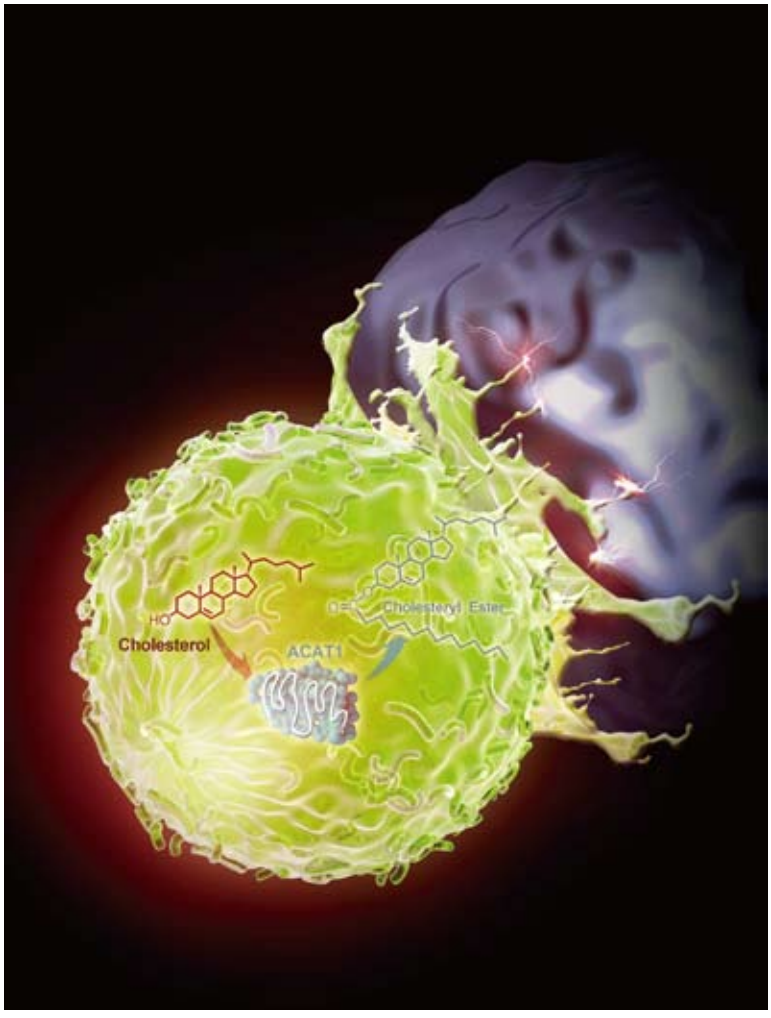
SIBCB Researchers Reveal a New Way to Potentiate T-cell Antitumor Immunity

On March 17, 2016 (Beijing time), *Nature* published online a research paper entitled "Potentiating the antitumour response of $CD8^+$ T cells by modulating cholesterol metabolism", authored by a team of researchers led by Profs. XU Chenqi and LI Boliang at the Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. In the paper the authors reported that inhibiting cholesterol esterification can potentiate the antitumor activity of $CD8^+$ T cells (also known as killer T cells), marking the discovery of a novel way of improving T cell function, which might be used as a complement to current cancer immunotherapies, such as immune checkpoint blockade.

As key players of the immune system, T cells provide tumor surveillance and have direct antitumor effects. On the other hand, tumors can escape T-cell attack, however, 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



In their latest research, a joint team led by Profs. XU Chenqi and LI Boliang at the Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences, CAS discovered that inhibiting cholesterol esterification can potentiate the antitumor activity of $CD8^+$ T cells (also known as killer T cells). (Picture by courtesy of Profs. XU and LI)

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

Profs. XU and LI's team investigated T-cell antitumor immunity from a new perspective. Based on previous research, they hypothesized that modulating T-cell metabolism can make killer T cells more "metabolically fit" to fight with tumor cells. As a key component of membrane lipids, cholesterol is important for T cell signalling and function. The researchers found that inhibiting the cholesterol esterification enzyme ACAT1 can increase the plasma membrane cholesterol level and therefore promote T-cell signalling and killing processes. They hence tried to use a small molecule inhibitor of ACAT1 called avasimibe to treat cancer in mouse tumor models and found it had good antitumor effect. Further, they discovered that a combination of avasimibe and anti-PD-1 antibody, a checkpoint blockade drug, showed even better antitumor effect. As a result, they successfully identified ACAT1 as a promising drug target, opening a new horizon of cancer immunotherapy. Given the fact that avasimibe had been tested in clinical trials to treat atherosclerosis and demonstrated a good human safety profile, it could be a promising drug candidate for cancer immunotherapy.

Other researchers from China and USA also contributed to this work, including Dr. LIU Xiaolong from SIBCB, Dr. LIU Wanli from Tsinghua University, Dr. SONG Baoliang from Wuhan University, Dr. ZHOU Penghui from Sun Yat-sen University Cancer Center, Dr. Shaocong Sun from The University of Texas MD Anderson Cancer Center, and Dr. Ta-Yuan Chang from Geisel School of Medicine at Dartmouth. This work was supported by grants from the National Natural Science Foundation of China, the Strategic Priority Research Program of the Chinese Academy of Sciences, the Ministry of Science and Technology of China, and Shanghai Science and Technology Committee. Technically this work was also supported by the Integrated Laser Microscopy Facility at the National Center for Protein Science in Shanghai, and SIBCB core facilities, namely the Animal Core Facility, Cell Biology Core Facility and Molecular Biology Core Facility.