Cancer immunotherapy: killers on sterols

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Immunotherapy for cancer has gone from a dream to a reality in recent years with the approval of several potent checkpoint blockade drugs that boost T lymphocyte (T cell) responses to multiple types of cancer and successful trials based on engineering a patient’s own T cells to attack B lineage leukemia and lymphomas. In this issue of Nature, Yang and colleagues propose a new way to boost the function of anti-tumor T cells using a metabolic trick to increase their plasma membrane cholesterol. The important role of plasma membrane cholesterol in T cell activation has been known about for a long time and relates in part to fundamental roles of cholesterol in plasma membrane organization that are essential to the way T lymphocytes recognize tumor cells through the T cell receptor (TCR). Yang et al show for the first time that a drug targeting an enzyme critical for cholesterol storage and transport paradoxically stimulates cholesterol synthesis in CD8+ “killer” T cells. Putting the killer cells on higher cholesterol boosts the immune attack on melanoma and lung cancer cells in preclinical animal models.

While it’s been clear that lowering plasma membrane cholesterol experimentally desensitizes T cells, and modest increases can enhance T cell responses in vitro, the range for cholesterol reduction achieved by common cholesterol lowering drugs does not lead to clinical immunosuppression. Similarly, there are no therapeutic approaches that purposefully increase cellular cholesterol, and as such, there has been no obvious way to boost immune system function by increasing cholesterol without toxicity. Yang et al started their investigation with genetically modified T cells from mice lacking acetyl-CoA acetyltransferase 1 (ACAT1), one of two enzymes that generates cholesterol esters—the form of cholesterol stored in lipid droplets and transported between cells in low density lipoproteins. The liver and gut use ACAT2, whereas most cells in the body, including T cells, express some level of ACAT1. Interestingly, data from the Immgen consortium (immgen.org) reveals that developing T cells express higher levels of ACAT2, which may explain the normal T cell development in mice with ACAT1 deficient T cells. Yang et al found that the ACAT1 deficient killer T cells up-regulated cholesterol biosynthesis enzymes. This paradoxical elevation of cholesterol synthesis in response to loss of cholesterol esterification selectively in the killer T cells is fortuitous, as many negative consequences of immune cell hyperactivity and a component of immune suppression in cancer development is linked more to CD4+ T cell subsets, which didn’t show elevated cholesterol. Hyperactive killer T cells can drive immunopathology, but none was noted in the study. It will be interesting to further understand the distinct metabolic regulation in killer T cells that lead to these outcomes.

Yang et al go on to show that the sterol-enhanced killer T cells responded to target recognition with larger T cell receptor clusters, enhanced signaling through adapters with affinity for cholesterol enriched membrane domains and faster formation of immunological synapses. The immunological synapse is the
point of embrace between the T cell and tumor cell that is important for killing the tumor and destruction of tumor associated infrastructure. Rapid formation of the immunological synapse enhances effector function. Signatures of T cell activation, particularly the phosphorylation of linker of activated T cells (LAT), were enhanced in ACAT1 deficient killer T cells. LAT is an adapter protein with a lipid modification that localizes it to distinct, cholesterol dependent nanoclusters that join with T cell receptor rich nanoclusters to form signaling microclusters. Increased cholesterol in ACAT1 deficient killer T cells appeared that join with T cell receptor rich nanoclusters to form signaling microclusters. They show that transferring tumor antigen specific ACAT1 deficient ACAT1 deficient killer T cells protected the host against the tumors better than wild type killer T cells. These results suggested that deleting ACAT1 in engineered killer T cells might be a useful addition to adoptive immunotherapy approaches, although they didn't explore this avenue further. Yang et al went on to investigate the potential to target ACAT with a small molecule to see if they could achieve similar benefits pharmacologically.

Avasimibe is a non-selective ACAT inhibitor that was found to be safe for short-term treatment in humans, but failed to have an impact on cardiovascular disease. Therefore, it has not been approved for use in humans, but could potentially go into trials for other indications and has the advantage of being administered in a convenient pill. With the potential for a positive impact on killer T cell responses, Yang et al tested avasimibe on in vitro T cell functions and in animal cancer models. They found that avasimibe phenocopied ACAT1 deficiency for T cell functional effects in vitro, including impacting nanoscale clustering of the TCR, and significantly increased survival of mice in melanoma and lung cancer models. In addition, avasimibe effects were additive when combined with anti-PD-1 based checkpoint blockade in the animal models. Anti-PD-1 checkpoint inhibitors have been approved for use in humans in melanoma, lung cancer and kidney cancer. While both avasimibe and anti-PD-1 enhance immunological synapse formation, the specific mechanisms are sufficiently distinct to have additive effects in vivo. Some cancer patients fail to respond to checkpoint blockade such that there is room to improve on these breakthrough therapies. It's exciting to speculate that Yang et al's basic observations and pre-clinical data may be a first step toward a pill for boosting killer T cells in anti-cancer and anti-viral therapies.


Tumor cell

Killer T cell

Cholesterol

HLA

ACAT1

TCR

LAT

Immunological synapse

Toxins

PD-L1

PD-1

amisibime

α-PD-1

Cholesterol Ester

Toxins

ACAT1

Cholesterol