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# Modulating lipid metabolism improves tumor immunotherapy

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## ABSTRACT

Immunotherapy has progressed significantly in cancer treatment; however, several factors influence its outcomes. Abnormal lipid metabolism, which is frequently observed in cancers, promotes tumor proliferation, invasion, and metastasis. Li *et al* from the Medical Oncology Department of Chongqing University Cancer Hospital constructed a lipid metabolism scoring system and reported that MK1775 inhibited fatty acid oxidation in tumor-associated macrophages and enhanced T-cell infiltration, further enhancing the efficacy of immunotherapy. This study demonstrated the critical role of lipid metabolism scoring system and lipid metabolism in immunotherapy. Currently, the metabolism of lipids, such as fatty acids, phospholipids, and cholesterol, has been reported to affect the tumor microenvironment by regulating immune cells, including T cells, natural killer cells, and macrophages. These metabolic changes can impair the efficacy of immunotherapy, resulting in tumor progression. Consequently, lipid metabolism emerges as an important immune regulator for improving immunotherapeutic outcomes and provides a novel and powerful strategy for tumor combination therapy.

Immunotherapies, such as immune checkpoint blockade, have demonstrated breakthrough success in cancer treatment. Anti-programmed cell death protein-1 (PD-1) therapy, approved for clinical applications, is a type of immune checkpoint blockade that specifically binds to PD-1 in T cells to prevent its interaction with programmed death-ligand 1, thereby enhancing T-cell anti-tumor function and eliminating tumor cells. However, many patients do not achieve optimal clinical responses. Decreased antitumor function of T cells, primarily influenced by the tumor microenvironment (TME), is critical. Many factors within the TME, including immunosuppressive elements and abnormal metabolism, restrict the antitumor function of T cells. Li *et al* developed a lipid metabolism scoring system using the data from The Cancer Genome Atlas, identifying that abnormal lipid metabolism in the TME affects tumor progression. They screened drugs that modulated lipid metabolism in the TME to enhance anti-PD-1 treatment.[1] The construction of a lipid metabolism-related model is beneficial for predicting immunotherapy efficiency.[2] These demonstrate that establishing a unique lipid metabolic scoring system facilitates a better understanding of the metabolic status of patients with cancer, enabling targeted and precise treatment.

Lipid metabolism is an important process by which cells acquire energy, maintain cellular membranes, and perform normal signal transduction. Cellular lipids mainly comprise fatty acids, phospholipids, and cholesterol. In cancer, lipid metabolism is associated with tumor progression and immunosuppression.[3] Li *et al* reported that DKK1, ANLN, and CCNA2 are highly expressed at the tumor site and are associated with poor prognosis. MK1775 modulates lipid metabolism, revealing that it inhibits fatty acid oxidation (FAO) to enhance T-cell infiltration and improve anti-PD-1 efficacy.[1] These findings demonstrate that targeting lipid metabolism reprogramming can effectively improve the efficacy of immunotherapy. Thus, there is an urgent need to explore the correlation between lipid metabolism and the tumor immune system and to discover potent lipid metabolic targets to enhance immunotherapy outcomes, as described in figure 1.

## FATTY ACID METABOLISM

Fatty acids are the major lipids in cells, essential for the synthesis of phospholipids and providing energy for FAO. The accumulation of long-chain fatty acids (LCFAs) in the TME can lead to $CD8^+$ T-cell dysfunction, exacerbated by the downregulation of very long-chain acyl-CoA dehydrogenase in these cells.[4] Linoleic acid, a fatty acid, enhances T-cell antitumor function by improving mitochondrial metabolism and the calcium signaling pathway.[5] In addition, microbiota-derived short-chain fatty acids promote T-cell receptor signaling and increase effector cytokine secretion, thereby improving the antitumor function of T cells.[6] These results indicate that altering the composition of fatty acids in the TME can enhance T-cell antitumor function

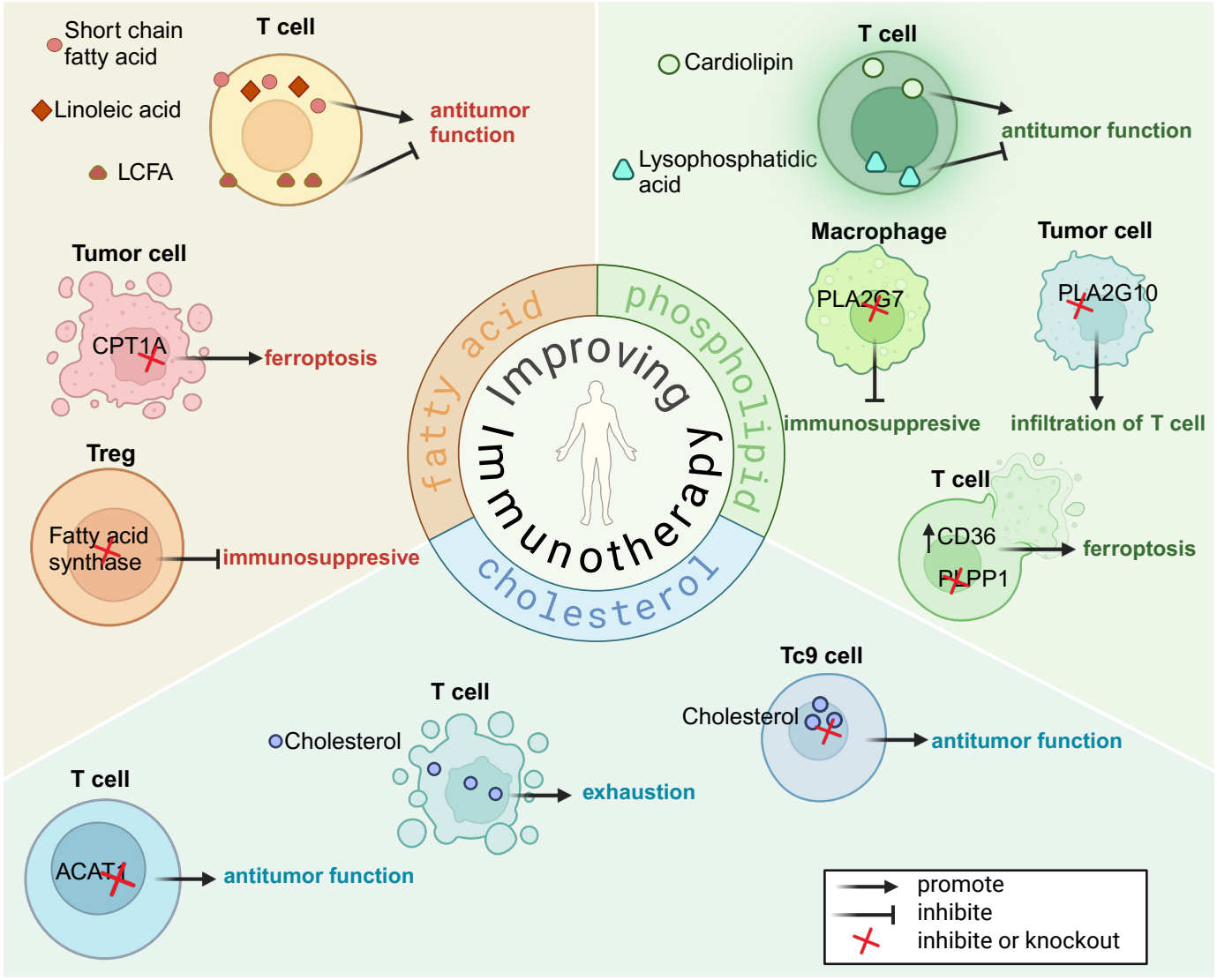


**Figure 1** Intervention of lipid metabolism to improve immunotherapy. Fatty acid metabolism plays a pivotal role in enhancing the antitumor function of T cells. The exogenous addition of fatty acids, including short-chain fatty acids and linoleic acid, or the reduction of LCFA can bolster the antitumor function of T cells. Inhibiting the expression of CPT1A in tumor cells promotes ferroptosis. The inhibition of fatty acid synthase restricts the immunosuppressive effects of Treg. Phospholipid metabolism significantly impacts the function of different cells. Elevating cardiolipin levels or reducing lysophosphatidic acid can enhance the antitumor function of T cells. By targeting specific molecules, such as PLA2G7 in macrophages, PLA2G10 in tumor cells, and CD36 and PLPP1 in T cells, immunotherapy can be further potentiated. Additionally, modulating cholesterol metabolism also plays a crucial role. Downregulating cholesterol in TME or inhibiting ACAT1 in T cells can boost the antitumor function of T cells. Reducing cholesterol levels enhances the functionality of Tc9 cells. ACAT1, Acyl-CoA cholesterol acyltransferase 1; CPT1A, carnitine palmitoyl transferase 1A; LCFA, long-chain fatty acids; PLA2G7, phospholipase A2 group 7; PLA2G10, phospholipase A2 group 10; PLPP1, phospholipid phosphatase 1; Tc9, interleukin (IL)–9-producing cytotoxic T; TME, tumor microenvironment; Treg, regulatory T cell.

and boost the efficacy of immunotherapy. In addition, the regulation of enzymes involved in fatty acid metabolic processes can affect the tumor immune system and enhance the efficacy of immunotherapy. For example, targeting carnitine palmitoyl transferase 1A synergizes with immunotherapy by stimulating NRF1/GPX4 and downregulating ACSL4 in tumor cells, leading to ferroptosis.[7] Enhancing FAO endows T cells with energy to maintain their antitumor function by upregulating the expression of acetyl-CoA carboxylase.[8] Restricting fatty acid synthase expression in regulatory T cells (Tregs) inhibits tumor growth.[9] Collectively, these metabolic enzymes represent important targets for enhancing the efficacy of immunotherapy.

Moreover, mitochondria are important sites for FAO in T cells. Tumor-infiltrating T cells require FAO to maintain cellular functions in nutrient stress conditions.[8] Mitochondrial structure and function of T cells in TME are impaired due to the loss of peroxisome proliferator-activated receptor-gamma coactivator 1α.[10] $CD8^+$ T cells acquired mitochondria from bone marrow stromal cells, exhibiting enhanced survival rate and function,[11] proving

that enhancing mitochondria in T cells is beneficial for improving the function of T cells. Although enhancing mitochondria can improve T-cell function, there is currently a lack of effective targets for targeting mitochondria that can be combined with immunotherapy, necessitating further exploration in future research.

## PHOSPHOLIPID METABOLISM

Phospholipids are the main components of cell membranes, maintaining membrane integrity; however, an increasing number of studies have shown that phospholipids are involved in regulating the immune system. Increased cardiolipin levels maintain and enhance T-cell function by boosting vascular endothelial growth factor B signaling or increasing the cardiolipin-synthesizing enzyme protein tyrosine phosphatase mitochondrial 1.[12 13] Modulating the metabolites and enzymes involved in sphingolipid metabolism helps maintain immune system balance. For example, sphingosine 1-phosphate maintains T-cell survival,[14] sphinganine promotes Treg accumulation,[15] and sphingomyelin sustains the cytotoxicity of natural killer cell.[16] Additionally, phospholipase A2 (PLA2) group 7 is highly expressed in intratumoral macrophages to promote immunosuppression, while PLA2 group 10, expressed in tumor cells, inhibits T-cell infiltration.[17 18] These results demonstrate that restraining the expression of PLA2 group 7 and PLA2 group 10 can optimize the immune system within the TME, thereby augmenting the efficacy of immunotherapy. Moreover, lysophosphatidic acid accumulates in the TME and induces T-cell exhaustion.[19] Thus, these enzymes or metabolites in the phospholipid metabolic pathway can regulate the tumor immune system and have the potential to synergistically enhance immunotherapy efficacy.

Increased unsaturated phospholipid levels impair T-cell antitumor function by inducing ferroptosis. $CD8^+$ T cells upregulate CD36, which promotes the uptake of polyunsaturated fatty acids and oxidized low-density lipoprotein, resulting in the accumulation of unsaturated phospholipids.[20] CD36 is also highly expressed in Tregs, promoting Treg adaptation to the lactate-rich TME and exerting immunosuppressive functions.[21] In addition, our previous study found that phospholipid phosphatase 1 (PLPP1) was downregulated in intratumoral $CD8^+$ T cells, enhancing unsaturated phospholipid levels and promoting ferroptosis. The PLPP1 knockout restricts the efficacy of anti-PD-1 therapy.[22] The antitumor function of T cells can be effectively restored by blocking CD36 or PLPP1, which are novel targets that reduce unsaturated phospholipids and ferroptosis.

## CHOLESTEROL METABOLISM

In activated $CD8^+$ T cells, cholesterol levels in whole cells and plasma membranes are significantly increased. Acyl-CoA cholesterol acyltransferase 1 (ACAT1) is the primary enzyme involved in cholesterol esterification in $CD8^+$ T cells. Knockout of ACAT1 or the use of an ACAT1 inhibitor significantly increased cholesterol levels in the plasma membrane of $CD8^+$ T cells, thereby enhancing the activation signal of these cells and inhibiting tumor growth.[23] Analysis of the cholesterol atlas in the TME has revealed that T cells exhibit impaired proliferation, enhanced apoptosis, and low cholesterol levels, which were affected by oxysterol-mediated reciprocal alterations in the liver X receptor and sterol regulatory element-binding protein 2 pathways.[24] However, cholesterol accumulates in the TME, where high concentrations induce the upregulation of inhibitory molecule expression and the downregulation of effective molecules through endoplasmic reticulum stress-X-box binding protein 1-dependent pathways, resulting in $CD8^+$ T-cell exhaustion.[25] Hence, improving cholesterol levels in T cells and decreasing cholesterol levels in the TME provide a robust antitumor function to augment immunotherapy outcomes.

Cholesterol is a key regulator of the differentiation and function of interleukin (IL)−9-producing cytotoxic T (Tc9) cells and can inhibit IL-9 expression by activating liver X receptors. Notably, the cholesterol content in Tc9 cells is lower than that in Tc1 cells. Adoptive transfer of tumor-specific Tc9 cells in mouse melanoma models elicits a stronger antitumor response compared with that in classical Tc1 cells.[26] This study highlights the negative regulatory effect of cholesterol on the antitumor function of T cells. Further research is needed to explore how regulating cholesterol content in T cells can enhance their antitumor function and augment immunotherapy outcomes.

## CONCLUSION

Current research has demonstrated that targeting a single lipid metabolism pathway in specific cells can effectively enhance the efficacy of immunotherapy. However, tumor tissue is a complex microenvironment, where the application of a single-target drug may lead to metabolic changes in cells other than the target cells. Furthermore, the same metabolic pathway may exert opposite regulatory effects in tumor cells, immunosuppressive cells, and immune effector cells. These factors limit the development and application of lipid metabolism targets. Therefore, an important consideration for us is how to improve the targeting specificity of lipid metabolism drugs.

Although lipid metabolism is crucial for maintaining the balance of the immune system, the current drug development for ideal lipid metabolic targets is inadequate. The lipid metabolic scoring model established based on patients' sequencing data has important clinical significance in screening effective metabolic targets and boosting the development of immunotherapy. Despite existing studies identifying potential lipid metabolic targets and revealing their regulatory mechanisms, whether these metabolic targets can effectively improve the efficacy of immunotherapy requires comprehensive

analysis. Discovering and identifying ideal lipid metabolic targets to improve immune therapy require mechanistic studies, preclinical models, and careful evaluation of clinical trials. With advancements in biotechnology, tools such as CRISPR libraries, organoids, biomaterials, and artificial intelligence can now be used for targeted screening and verifying. These technological platforms contribute to the rapid acquisition of lipid metabolic targets to enhance immunotherapy efficacy. The development of these lipid metabolism targets enables individualized treatment for patients, effectively enhancing the efficacy of tumor immunotherapy.

**Correction notice** This article has been corrected since it was first published online. In the abstract, the word 'reduced' has been changed to 'enhanced' in the following sentence: 'Li et al. from the Medical Oncology Department of Chongqing University Cancer Hospital constructed a lipid metabolism scoring system and reported that MK1775 inhibited fatty acid oxidation in tumor-associated macrophages and reducedenhanced T -cell infiltration, further enhancing the efficacy of immunotherapy'.

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