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REVIEW

The influence of fatty acid metabolism on T cell function in lung cancer

Jessica Petiti[1], Ludovica Arpinati[2], Alessio Menga[3,4] and Giovanna Carrà[5,6,7]

1 Division of Advanced Materials Metrology and Life Sciences, Istituto Nazionale di Ricerca Metrologica (INRiM), Turin, Italy
2 Department of Biomolecular Sciences, The Weizmann Institute of Science, Rehovot, Israel
3 Department of Health Sciences, University of Eastern Piedmont, Novara, Italy
4 Center for Translational Research on Autoimmune & Allergic Diseases – CAAD, Novara, Italy
5 San Luigi Gonzaga Hospital, Orbassano, Italy
6 Department of Clinical and Biological Sciences, University of Turin, Italy
7 Molecular Biotechnology Center (MBC), University of Turin, Italy

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Correspondence
G. Carrà, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Italy; Molecular Biotechnology Center (MBC), University of Torino, Via Nizza, 52, Turin 10126, Italy
Tel: +39 3204909579
E-mail: giovanna.carra@unito.it
and
A. Menga, Center for Translational Research on Autoimmune & Allergic Diseases – CAAD, Corso Trieste 15/A, Novara 28100, Italy
Tel: +39 3382778472
E-mail: alessio.menga@uniupo.it

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The tumor microenvironment (TME) is a complex ecosystem, encompassing a variety of cellular and non-cellular elements surrounding and interacting with cancer cells, overall promoting tumor growth, immune evasion, and therapy resistance. In the context of solid tumors, factors, such as hypoxia, nutritional competition, increased stress responses, glucose demand, and PD-1 signals strongly influence metabolic alterations in the TME, highly contributing to the maintenance of a tumor-supportive and immune-suppressive milieu. Cancer cell-induced metabolic alterations partly result in an increased fatty acid (FA) metabolism within the TME, which strongly favors the recruitment of immune-suppressive M2 macrophages and myeloid-derived suppressor cells, crucial contributors to T-cell exhaustion, tumor exclusion, and decreased effector functions. The drastic pro-tumoral changes induced by the tumor metabolic rewiring result in signaling loops that support tumor progression and metastatic spreading, and negatively impact therapy efficacy. As tumor- and immune metabolism are increasingly gaining attention due to their potential therapeutic implications, we discuss the effects of altered lipid metabolism on tumor progression, immune response, and therapeutic efficacy in the context of lung cancer. In particular, we focus our analysis on the tumor-induced

Abbreviations
ACAT1, acetyl-CoA acetyltransferase 1; ACC1/ACC2, acetyl-CoA carboxylase 1/2; ACLY, ATP citrate lyase; ACSL4, acyl-CoA synthetase long-chain family member 4; AKT, protein kinase B; AP-1, activator protein 1; APC, antigen-presenting cell; CPT1a, carnitine palmitoyltransferase 1a; CR, calorie restriction; CTL, cytotoxic T lymphocytes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; ER, endoplasmic reticulum; FA, fatty acid; FABP, fatty acid-binding protein; FAO, fatty acid oxidation; HIF-1α, hypoxia-inducible factor 1-alpha; ICIs, immune checkpoint inhibitors; IFN-γ, interferon-gamma; IL-15, interleukin-15; LAG-3, lymphocyte-activation gene 3; LUAD, lung adenocarcinomas; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; mTORC1/mTORC2, mechanistic target of rapamycin complex 1/2; NCT, National Clinical Trial; NK, natural killer; Nrf2, nuclear factor-like 2; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PI3K, phosphatidylinositol-3 kinase; PPAR, peroxisome proliferator-activated receptor-α; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SRC, spare respiratory capacity; SREBP, Sterol regulatory element-binding proteins; STAT3, signal transducer and activator of transcription 3; TCR, T-cell receptor; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; Tregs, regulatory T cells; ULK1, Unc-51 like autophagy activating kinase 1; VEGF, vascular endothelial growth factor; WGCNA, weighted gene co-expression network analysis.

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metabolic alterations experienced by T lymphocytes and the possible strategies to overcome immunotherapy resistance by targeting specific metabolic pathways in T cells.

Introduction

Lung cancer, ranking among the most pervasive and deadly diseases worldwide, represents a remarkable global health challenge. According to the World Cancer Research Fund, lung cancer accounted for nearly 2 million new cases and 1.8 million deaths in 2020, becoming the most common cancer diagnosis and leading cause of cancer-related mortality [1]. Due to its insidious onset, frequently characterized by an asymptomatic progression, it has earned the ominous moniker of *silent killer*.

The primary cause of lung cancer is tobacco smoking, the most significant single risk factor [2]. Exposure to secondhand smoke, occupational hazards, such as asbestos or radon, as well as mutational burden are other substantial contributing factors [3–5]. In fact, recent data suggest that various genetic mutations can facilitate susceptibility to lung cancer even in the absence of significant exposure to known carcinogens [6–9].

However, among the multitude of factors contributing to lung cancer formation, metabolic reprogramming stands out as a hallmark of the disease [10].

The tumor microenvironment (TME) is a complex ecosystem, encompassing a variety of cellular and non-cellular elements, including immune cells, blood vessels, fibroblasts, and extracellular matrix (ECM) components that surround and interact with cancer cells to promote tumor growth by facilitating tumor immune evasion, cancer cell proliferation, and dissemination at distant sites [11–14]. The highly dynamic TME plays a pivotal role in facilitating metabolic reprogramming, with nutrient availability emerging as a crucial factor. For instance, in hypoxic environments, characterized by limited oxygen availability, tumor cells can shift from aerobic to anaerobic glycolysis to generate energy [15]. Conversely, in nutrient-rich environments, tumor cells may upregulate pathways involved in nutrient uptake and metabolism to support their rapid growth and proliferation. In this context, the TME provides essential nutrients and signaling cues to fuel their rapid growth, as evidenced by numerous studies [16,17]. Additionally, the metabolic reprogramming undergone by cancer cells can reciprocally influence the TME, creating a niche that promotes tumor invasion and immune evasion. Therefore, metabolic alterations are not merely passive outcomes of malignant transformation; rather, they actively contribute to cancer progression by furnishing the necessary building blocks for sustained cell proliferation and survival. A well-known metabolic change is the Warburg effect, wherein cancer cells preferentially utilize aerobic glycolysis, even in the presence of oxygen. This metabolic shift is facilitated by upregulated glucose transporters (such as GLUT1 and GLUT2), leading to increased glucose uptake and high glycolytic activity. Cancer cells often convert pyruvate to lactate, creating an acidic microenvironment that promotes tumor invasion and metastasis [18–21]. Alterations in mitochondrial function and antioxidant pathways, increased amino acid uptake (e.g., glutamine), hypoxia, and deregulation of nutrient-sensing pathways, like mTOR and AMPK, are frequently observed in cancer cells and contribute to the maintenance of a tumor-promoting and immune-suppressive TME [22].

Significant progress has been made in dissecting the TME to better understand cancer progression and improve therapy response. Effective therapeutic options for lung cancer remain an unmet clinical need. In fact, the high aggressiveness of lung cancer, the late diagnosis and lack of preventive screenings, as well as the poor response to current treatments, mean that surgical resection currently remains the most effective treatment; thus, surgical resection remains the best option [23].

When discussing novel therapeutic approaches for lung cancer, immunotherapy cannot be overlooked and it is intricately linked to the tumor dysregulated fatty acids (FA) metabolism, a hallmark of cancer. In fact, as cancer cells require lipids for membrane synthesis and signaling molecules, fatty acid synthesis (FAS)—including the overexpression of FA synthase (FASN)—is highly upregulated in cancer [24]. In the last 10 years, the field of immunometabolism has grown and highlighted the relationship between metabolism, particularly FA metabolism, in the differentiation and functional regulation of lymphocytes. Tumor cells generate significant quantities of FA via *de novo* synthesis, shaping a TME rich in FA that negatively impacts the functionality of tumor-suppressive cells,

such as effector T cells and M1-type macrophages. These significant changes foster the proliferation and recruitment of immunosuppressive Tregs and M2-like macrophages, contributing to the maintenance of an immune-excluded and tumor-supportive microenvironment [25]. In the context of ovarian cancer, the upregulation of fatty acid synthase (FASN) led to lipid accumulation in tumor-infiltrating dendritic cells (DCs), resulting in dysfunctional T-cell activity and impaired antitumor immune responses [26]. A different study showed that tissue-resident memory T (Trm) cells in gastric adenocarcinoma exhibit a preference for fatty acid oxidation (FAO) over glucose utilization for energy production [27], further underlining the role of FA metabolism in reshaping the TME.

Immunotherapy has exhibited remarkable efficacy in select cases [28–30]. Unlike traditional therapies that directly target cancer cells, immunotherapy harnesses the power of the patient's immune system to combat the disease. One of the remarkable aspects of immunotherapy is its potential for long-lasting responses [31,32].

This review aimed to highlight the crucial role of lipid metabolism in the context of lung cancer and to discuss its impact on the regulation of T-cell function. Understanding how metabolic changes impact cancer cell survival and/or immunotherapy efficacy may lead to the identification of novel therapeutic targets for lung cancer treatment. Furthermore, exploring the relationship between lipid metabolism and immune responses could open the way for innovative strategies to enhance the effectiveness of current therapies.

Understanding altered fatty acid metabolism in lung cancer

Lipids, comprising hydrophobic organic compounds, are vital for cell structure, function, and signaling. Cancer cells have increased lipid needs for membrane synthesis, energy production, and signaling essential for growth and metastasis [33].

Cells harness FA from various sources, either external, such as the diet, or internal through *de novo* lipogenesis, in which FAs are produced from nutrients like glucose and glutamine. Many cancer types exhibit elevated lipid uptake and storage, along with increased expression of proteins and enzymes involved in lipid metabolism. Additionally, cancer cells ramp up the synthesis of lipids, particularly phospholipids (PLs) and cholesterol, by boosting the activity and expression of crucial enzymes in their biosynthetic pathways, surpassing normal cell rates [34]. Importantly, alterations in lipid metabolism have surfaced as a significant characteristic that contributes to the advancement and spread of lung cancer [35].

One of the main consequences of an aberrant FA metabolism in cancer cells is the upregulation of lipogenesis, resulting in an excessive production of extracellular FA that leads to alterations in the TME and promotes tumor progression [36–38]. Elevated lipogenesis is driven by activated transcriptional regulators and overexpressed enzymes like SREBPs and FASN, respectively. In the context of lung cancer, SREBPs have been implicated in tumorigenesis and progression. Studies have shown that SREBP1 is overexpressed in lung cancer tissues and cell lines, and its expression correlates with poor prognosis [39,40]. SREBP1 promotes lung cancer cell proliferation, migration, and invasion by regulating the expression of genes involved in FAS, cholesterol synthesis, and lipid uptake. Additionally, SREBP1 has been shown to contribute to lung cancer cell survival and resistance to chemotherapy [41]. SREBPs are activated in response to growth factors and other signals in the TME, and are inducers of FASN gene expression [42,43]. FASN inhibitors have been considered a promising therapeutic strategy for their ability to limit tumor growth by inhibiting *de novo* lipogenesis. Recent findings from stable isotope tracing assays revealed that FASN inhibitors, such as GSK2194069 and orlistat, were able to completely block *de novo* FAS in multiple cancer cell lines, including the human lung cancer cell line H460 [44].

Reports indicate that increased lipogenesis is associated with transformation induced by hexavalent chromium [Cr(VI)]. Hexavalent chromium [Cr(VI)] is a well-known environmental carcinogen widely used in industrial processes, such as stainless steel production, welding, and pigment manufacturing [45,46]. Exposure to Cr(VI) has been linked to lung cancer, primarily due to its ability to induce cellular transformation through mechanisms involving oxidative stress and DNA damage [37,47,48]. *In vitro* studies reported a significant elevation in lipogenesis—detected by higher levels of palmitic acid—in three different human lung cancer cell lines (i.e., BEAS-2B, BEP2D, and WTHBF-6) following Cr(VI) exposure [37]. Furthermore, the Cr(VI)-transformed cells showed increased expression of key lipogenesis proteins, such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC1), and FASN [37].

As previously stated, cancer cells can also obtain FAs from external sources, primarily relying on exogenous FA uptake. In the context of lung cancer, this process is facilitated by the overexpression of various FA transporters, including CD36 and fatty acid-binding protein 4 (FABP4) [49,50]. Additionally,

cancer cells can accumulate FA in the form of cytoplasmic lipid droplets (LDs) to support cell proliferation and facilitate cell–cell communication [51–55]. Although there is currently limited available literature surrounding the role of LDs in lung cancer, recent evidence suggests that LD accumulation may facilitate lung cancer cell survival, and that an LD genetic-associated signature might serve as a prognostic tool for lung cancer patients [52,56,57]. Various transcriptional regulators of lipogenesis and lipid storage, including SREBP1 and PPAR-α, were found to be expressed in numerous human lung cancer cell lines (e.g., A549, H260, and H292), but not in WI-38 normal lung cells [52]. Additionally, lung cancer cells accumulated significantly larger amounts of LDs than normal lung cells following culture in a lipoprotein-deficient media [52]. Further analysis revealed that under starvation conditions (i.e., glucose and serum-free culture media), LD-containing lung cancer cells were able to proliferate at significantly higher rates compared with their LD-deficient counterparts [52], indicating a potential role for LD in facilitating cancer cell survival. Significantly higher amounts of LDs were recently detected in mouse-derived lung adenocarcinomas, characterized by high oxidative phosphorylation (OXPHOSHi) and FAO, compared with lung tumors with low OXPHOS and FAO [56]. Moreover, low glucose conditions significantly reduced lung cancer cell growth in OXPHOSLo cells, but did not impact OXPHOSHi cell proliferation, further underlining how LDs might facilitate cell survival [56].

Recent advances in genomic and metabolomic technologies have provided significant insights into the mechanisms driving lung cancer altered FA metabolism. Indeed, numerous mutations and copy number variations have been identified in upstream regulatory genes or signaling pathways that can lead to the overexpression of key enzymes involved in lipid metabolism [56]. Specifically, alterations in the expression of these enzymes are frequently driven by oncogenic signaling pathways, such as PI3K-AKT and mTOR, which are commonly activated in lung cancer [42] and can induce the overexpression of FASN, ACLY, and SCD1, associated with increased *de novo* FAS and membrane biosynthesis, as well as enhanced energy storage and intracellular signaling, all of which are critical for tumor growth and metastasis [41]. Additionally, epigenetic modifications, including DNA methylation and histone acetylation, have been shown to modulate the expression of critical lipid metabolism genes, further contributing to the metabolic reprogramming of cancer cells [16]. A recent metabolomic profiling of non-small-cell lung cancer (NSCLC) patient samples revealed the presence of distinct lipidomic signatures in lung cancer tissues compared with their normal counterparts [58], further indicating the existence of tumor-specific metabolic pathway rewiring. These profiles often show increased levels of saturated and monounsaturated FA, which are linked to increased membrane rigidity, altered intracellular signaling, and resistance to apoptosis [59,60]. Furthermore, studies using stable isotope tracing have demonstrated that lung cancer cells preferentially utilize glucose and glutamine for *de novo* FAS, highlighting the existence of a significant metabolic flexibility of cancer cells in constantly adapting to an ever-changing TME [61,62].

It is worth mentioning that the integration of genomic and metabolomic data can provide a more comprehensive understanding of how FA metabolism alterations can affect other components of the TME, such as immune cells. For example, the upregulation of lipid metabolism-related genes in lung cancer cells can result in the accumulation of immunosuppressive lipid species in the TME, impairing T-cell activation and promoting immune evasion [63,64]. Additionally, metabolomic profiling can help stratify patients based on lipid metabolic phenotypes, offering a personalized approach to target FA metabolism in lung cancer [65].

Considering these factors, integrating multi-omics approaches, and combining treatments that target lipid metabolism at various stages could emerge as a more effective therapeutic strategy for inhibiting lung cancer cell survival.

T lymphocytes and metabolism

T lymphocytes are essential components of the adaptive immune system, actively orchestrating immune responses against infections and diseases, while also maintaining immune memory and self-tolerance [66,67]. T cells are defined by the selective expression of T-cell receptors (TCRs), which enable them to recognize antigens presented by antigen-presenting cells (APCs) via major histocompatibility complexes I and II (MHC-I and MHC-II). T lymphocytes develop in the thymus from thymocyte progenitors and can differentiate into a variety of subsets, each characterized by different markers and functions [68,69]: αβ T cells, such as $CD4^+$ and $CD8^+$ T cells, γδ T cells, and natural killer (NK) T cells [70–72].

T-cell activation and differentiation

TCR-mediated activation of naïve $CD4^+$ and $CD8^+$ T cells triggers clonal expansion and differentiation

into specialized effector cells [68]. Upon activation, $CD8^+$ T-cell differentiate into cytotoxic T lymphocytes (CTLs), acquiring the ability to directly kill infected or malignant cells. Additionally, both $CD8^+$ and $CD4^+$ T cells can differentiate into antigen-specific memory T cells, which are primed for rapid effector responses upon re-exposure to the same antigen. $CD4^+$ T cells further diversify into various helper T-cell subsets (Th1, Th2, Th17, etc.) and regulatory T cells (Tregs), which play a pivotal role in maintaining peripheral immune tolerance. However, in the context of cancer, Tregs can hinder antitumor immunity due to their immunosuppressive functions [71,73].

Metabolic regulation of T cells

Our understanding of T-cell biology has dramatically expanded in recent decades, highlighting the intricate interplay of factors that influence T-cell fate and function, with metabolism emerging as a critical determinant [74,75]. Naïve T-cell activation involves complex TCR signaling, leading to the activation of ZAP-70, increased intracellular calcium levels, and the subsequent activation of the Ras-MAPK and PI3K-Akt pathways, driving survival, cell cycle progression, and metabolic reprogramming [76,77]. Activated T cells upregulate glycolysis to meet their energy demands, while transcription factors, such as NFAT, AP-1, and NF-κB orchestrate clonal expansion and effector differentiation [78].

Lipids, encompassing fats, oils, and PLs, are fundamental to cellular functions, serving as structural components, energy reserves, and signaling molecules [75]. In cancer, altered lipid metabolism, particularly increased FA availability, significantly affects T-cell activation, proliferation, and differentiation [79–81]. FA availability in the TME can drive Treg differentiation, thereby suppressing $CD8^+$ T-cell cytotoxicity and cytokine production [82]. Conversely, memory $CD8^+$ T cells rely on FAO for their longevity [83–85]. Overall, FA metabolism reshapes the TME composition, promoting the accumulation of immunosuppressive cells, such as macrophages, DC, and myeloid-derived suppressor cells (MDSCs), which in turn alter $CD8^+$ T-cell infiltration and function [86,87]. Aberrant FA metabolism can disrupt mTOR signaling, a central regulator of T-cell responses, impairing the balance between glycolysis and FAO, hindering protein translation, and skewing T-cell differentiation [88]. Additionally, increased FA metabolism can induce endoplasmic reticulum (ER) stress, which can facilitate T-cell apoptosis and therefore compromise proper antitumor immunity [89]. In summary, the intricate relationship between T-cell metabolism and function can be profoundly influenced by a lipid-enriched TME. Understanding the various T-cell metabolic adaptations is therefore critical for the development of novel therapeutic strategies that could help overcome immune therapy resistance.

Impact of the tumor microenvironment on fatty acid metabolism

The TME exerts a profound influence on FA metabolism within its boundaries, shaping the metabolic behavior of both tumor cells and immune cells. This influence is multifaceted, stemming from factors, such as nutrient availability, oxygen supply, and the presence of signaling molecules. The TME often presents an environment rich in FAs, generated by the heightened *de novo* lipogenesis in tumor cells [90,91]. This abundance of FAs can promote the accumulation of immunosuppressive cells, such as Tregs and M2 macrophages, while also impacting the functionality of effector T cells and M1-type macrophages [92,93]. Conversely, the TME can be glucose-poor due to the high glucose consumption of tumor cells [94]. This scarcity can lead to metabolic competition between tumor cells and immune cells, potentially influencing the balance between glycolysis and FAO in T cells [84]. The TME is often characterized by low oxygen levels (hypoxia) due to the rapid growth of tumor cells and the inadequate blood supply [95]. Hypoxia can induce metabolic reprogramming in both tumor cells and immune cells, leading to a shift toward anaerobic glycolysis and altered FA metabolism [96]. In response to nutrient deprivation and hypoxia, tumor cells often upregulate FAS and lipid storage to sustain their growth and survival [97]. Nutrient scarcity and hypoxia together can impair T-cell effector functions and promote T-cell exhaustion [98,99]. For instance, Klysz *et al.* [100] demonstrated that glutamine deprivation in tumors favors the development of regulatory T cells (Tregs) over effector T helper 1 (TH1) cells, even when TH1-promoting signals are present. This suggests that glutamine scarcity within the TME skews the immune response toward a more immunosuppressive state, potentially hindering antitumor immunity. Within the TME, activated $CD8^+$ T cells can enhance FAO to adapt to the nutrient-poor and hypoxic conditions [84]. However, chronic antigen stimulation can lead to $CD8^+$ T-cell exhaustion, characterized by increased lipid uptake and FAO, potentially driven by PD-1 signaling [101]. The TME can also influence $CD4^+$ T-cell subsets. Regulatory T cells (Tregs) exhibit a preference for FAO, while Th1, Th2, and Th17 cells primarily rely on glycolysis [102,103]. The TME's metabolic milieu can shape the balance between these subsets, influencing the overall immune response [104].

Moreover, the TME is rich in signaling molecules, such as PD-1 ligands, which can further alter FA metabolism. PD-1 signaling has been shown to inhibit glycolysis while promoting FA oxidation in T cells, potentially contributing to T-cell exhaustion and immune suppression [105,106]. The TME also contains other signaling molecules, such as cytokines and growth factors, which can influence FA metabolism in both tumor cells and immune cells [107]. These signals can promote FAS, FA uptake, or FA oxidation, depending on the specific context.

Fatty acid metabolism in CD8$^+$ T-cell subsets

FA metabolism plays a pivotal and multifaceted role in shaping the fate and function of CD8$^+$ T cells, directly impacting their ability to combat tumors. This metabolic landscape varies significantly across the distinct stages of CD8$^+$ T-cell differentiation and activation, influencing their survival, proliferation, and effector functions within the challenging TME.

Memory CD8$^+$ T cells

The generation and maintenance of memory CD8$^+$ T cells (CD8$^+$ Tmem) are paramount for long-term immune surveillance and protection against pathogens and tumors [108]. These cells exhibit a distinct metabolic profile characterized by a heightened reliance on FAO for sustained survival and robust functionality. Memory CD8$^+$ T cells maintain a substantial spare respiratory capacity (SRC), reflecting their enhanced mitochondrial capacity for FAO [109]. This metabolic flexibility enables rapid upregulation of oxidative metabolism upon antigen re-encounter, facilitating swift and potent effector responses. Notably, tissue-resident memory T (Trm) cells within the TME also depend on FAO for energy production and lose functionality when deprived of FAs [27]. Several factors contribute to this enhanced FAO phenotype. Interleukin-15 (IL-15) and CD28 costimulatory signaling promote mitochondrial biogenesis and upregulate the expression of carnitine palmitoyltransferase 1a (CPT1a), a key enzyme in FAO, thus augmenting SRC [110,111]. Adenosine monophosphate-activated protein kinase (AMPK) further reinforces this metabolic program by inhibiting *de novo* FAS and promoting long-chain FA oxidation (LC-FAO) through phosphorylation of ACC1 and ACC2 [112]. Furthermore, AMPK activates PGC1α, a master regulator of mitochondrial biogenesis, via phosphorylation of ULK1 kinase [113]. The critical importance of LC-FAO in memory CD8$^+$ T-cell development is underscored by observations in TNF receptor-associated factor 6 (TRAF6)-deficient T cells, which exhibit impaired AMPK activation, reduced LC-FAO, and a failure to adopt a memory phenotype [114]. Conversely, mTORC1 and mTORC2 signaling, while essential for T-cell activation, may hinder the transition from effector to memory phenotype by suppressing FAO [115,116] (Fig. 1). This is further supported by findings in T-cell-specific AMPKα1 knockout mice, where antigen-specific T cells proliferate normally but fail to generate robust memory responses [117].

Naïve and effector CD8$^+$ T cells

In contrast to memory T cells, quiescent CD8$^+$ T cells predominantly rely on pyruvate and FA for energy production through oxidative phosphorylation (OXPHOS). However, upon activation and antigen encounter, they prefer to upregulate FAS through the phosphatidylinositol-3-OH kinase (PI3K)-protein kinase B (Akt) signaling pathway [118,119]. Activated Akt induces FAS-related genes and promotes *de novo* FAS [120]. It directly phosphorylates and activates ACLY, converting citrate into acetyl-CoA, and also activates nuclear factor-like 2 (Nrf2) to enhance NADPH production, both of which are essential for FAS by FASN [121–123]. Interestingly, within a nutrient-depleted and hypoxic TME, effector CD8$^+$ T cells adapt their metabolism by enhancing FAO through peroxisome proliferator-activated receptor-α (PPAR-α) signaling [124] (Fig. 1). While the direct link between SREBPs and CD8$^+$ T cells in lung cancer remains underexplored, recent research suggests a potential role for SREBPs in regulating CD8$^+$ T-cell function and immunity. A study by Kidani *et al.* [125] demonstrated that SREBPs-deficient CD8$^+$ T cells exhibit impaired effector function. Mechanistically, SREBP signaling deficiency led to decreased expression of genes involved in FAS and mitochondrial respiration, resulting in reduced ATP production and impaired CD8$^+$ T-cell activation.

Exhausted CD8$^+$ T cells

Chronic antigen stimulation within the TME can drive CD8$^+$ T cells into a state of exhaustion, characterized by impaired effector function and increased expression of inhibitory receptors, such as CTLA-4, PD-1, Tim-3, and LAG-3 [126]. These inhibitory receptors also modulate FA metabolism in exhausted CD8$^+$ T cells [127]. Research in NSCLC has revealed that PD-1^{hi} CD8$^+$ TILs exhibit increased lipid uptake and content compared with PD-1^{low} CD8$^+$ T cells [128]. Moreover, PD-1 ligand signaling has been shown to inhibit glycolysis

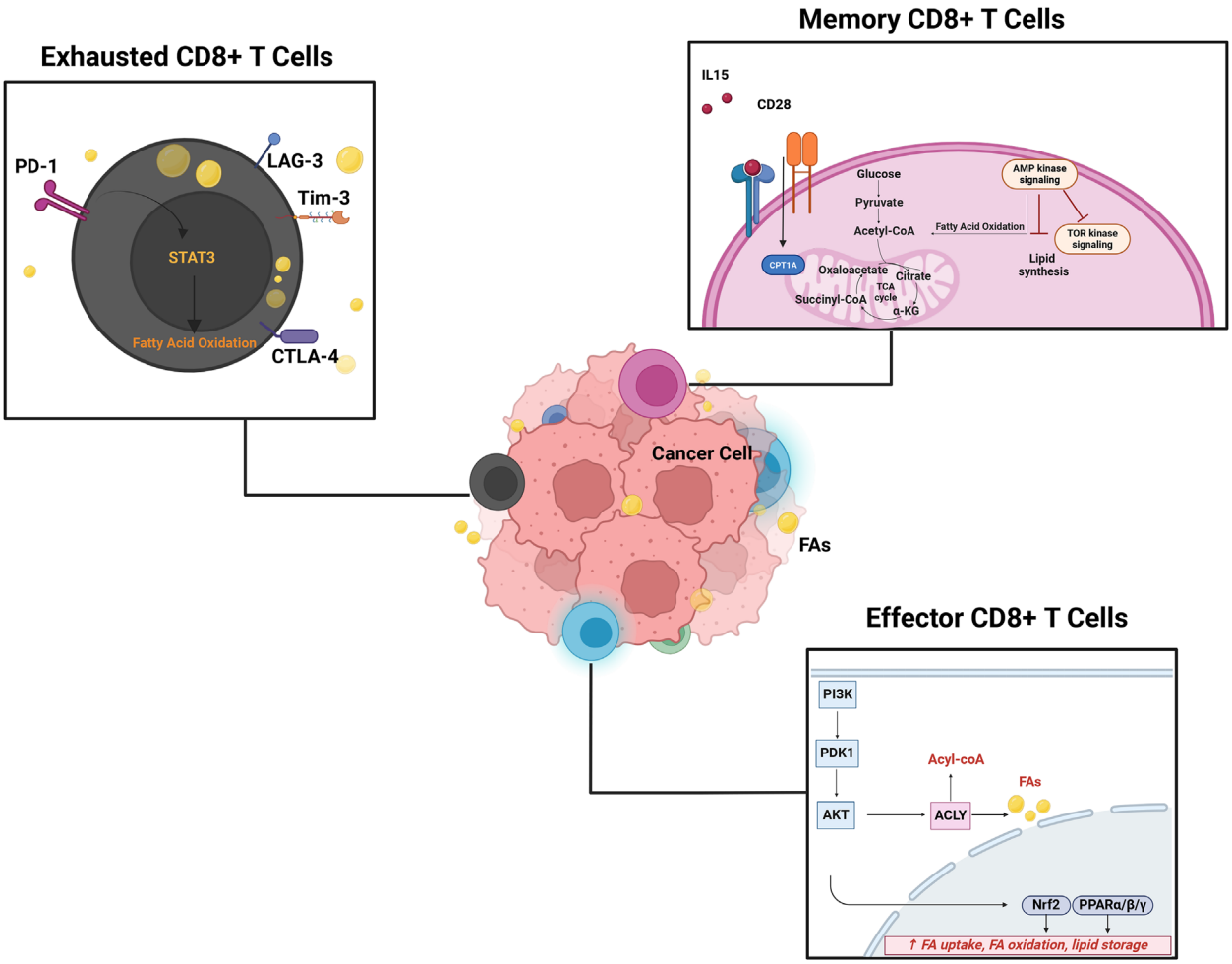

Fig. 1. Fatty acid metabolism in CD8$^+$ T-cell subsets. Memory CD8$^+$ T cells: Highlighted mitochondria indicate a reliance on fatty acid oxidation (FAO) for energy. Key molecules include CPT1a, AMPK, and PGC1α, with labels indicating enhanced mitochondrial capacity for FAO, Interleukin-15 (IL-15), CD28 signaling, and AMPK activation. Effector CD8$^+$ T cells: Upon activation, effector cells upregulate fatty acid synthesis (FAS), adapting to the nutrient-depleted TME by enhancing FAO. Key molecules include PI3K, Akt, ACLY, Nrf2, and PPAR-α, with labels for quiescent state OXPHOS, activation of *de novo* FA synthesis, and nutrient-depleted TME adaptation with enhanced FAO. Exhausted CD8$^+$ T cells: Characterized by high lipid uptake and content, these cells display chronic antigen stimulation and impaired effector function. Key molecules include PD-1, CTLA-4, Tim-3, LAG-3, and STAT3, with labels indicating increased lipid uptake and enhanced FAO via PD-1 signaling.

while promoting FAO in T cells by upregulating CPT1a expression [101]. In breast tumor lung metastasis, PD-1 ligand signaling also enhances FAO in CD8$^+$ T effector cells through STAT3 activation and concurrent suppression of glycolysis [129] (Fig. 1).

Overall implications

The metabolic landscape of CD8$^+$ T cells is dynamic and tightly regulated, adapting to the specific demands of different stages of differentiation and activation states. A comprehensive understanding of the intricate interplay between FA metabolism and CD8$^+$ T-cell function is crucial for developing innovative immunotherapies. By targeting these metabolic pathways, it may be possible to enhance antitumor immunity and overcome the immunosuppressive barriers imposed by the TME. Further research in this area holds the potential to unlock novel therapeutic strategies and improve outcomes for cancer patients.

Fatty acid metabolism in CD4$^+$ T cells

CD4$^+$ lymphocytes play important roles in health and disease, as they coordinate antigen response and immune memory [130]. CD4$^+$ T cells exhibit

diverse functions, giving rise to regulatory $CD4^+$ $CD25^+$ T cells (Treg) and conventional $CD4^+$ T helper (Th) cells, categorized into Th1, Th2, and Th17 subtypes [131–133]. Th1 cells, when mature, trigger immune responses against intracellular pathogens and autoimmunity by stimulating macrophages and $CD8^+$ Tc cells using interferon-γ (IFN-γ). Conversely, Th2 cells combat extracellular pathogens like helminths by activating eosinophils, basophils, and B cells with interleukin 4 (IL4) [134]. Finally, Th17 cells contribute to immune responses against extracellular fungal or bacterial infections by activating neutrophils via IL17 [132]. In the context of cancer, numerous studies have underscored how distinct CD4 T-cell subpopulations actively contribute to antitumor immunity rather than merely acting as auxiliary components. Tregs have garnered particular attention due to their potent immunesuppressive activity across various tumor types, promoting tumor progression and impeding the efficacy of anticancer therapies [135]. Conversely, Th1 and Th2 subsets have demonstrated antitumor functions by directly influencing cancer cell behavior and viability [136,137], or by releasing apoptotic factors that modify the recruitment of pro-tumoral macrophages to the tumor site [138]. Moreover, the high presence of Th1 in the TME positively correlated with better patient overall survival in multiple cancer types [139,140], further supporting their potential antitumor activity. However, not all T helper cells display clear antitumor activity, as Th17 was reported to display both tumor-supportive and tumor-suppressive functions, depending on the tumor type [141]. Various $CD4^+$ T-cell subsets derive their functions from distinct microenvironments, including their metabolic profiles, which drive specific patterns of differentiation [81]. For instance, Th1, Th17, and Th2 cells primarily depend on glycolysis [142], whereas Tregs prefer FAO. Following the immune response, most effector $CD4^+$ T cells undergo apoptosis, while some transition into memory T cells, which switch back to oxidative phosphorylation (OXPHOS) and FAO to sustain long-term immunity without relying on high glycolytic metabolism [102] (Fig. 2). The study by Tang *et al.* [143] is specifically centered on metabolism or, more precisely, on metabolism-related genes (MRGs) as prognostic markers for LUAD. Utilizing data from a LUAD dataset of 500 samples from The Cancer Genome Atlas (TCGA), a model based on four specific genes (BIRC5, PLK1, CDKN3, and CYP4B1) and Weighted Gene Co-Expression Network Analysis (WGCNA) revealed that patients categorized into the MRG subgroup showed significant associations with cell cycle-related pathways, increased infiltration of activated memory $CD4^+$ T cells, M0 macrophages, and neutrophils, and exhibited a more favorable response to immune checkpoint inhibitors (ICIs).

A study of single-cell sequencing on lung adenocarcinomas revealed metabolic heterogeneity among groups of lymphocytes based on their location. For instance, it was observed that certain pathway activities associated with immune depletion were notably activated in naïve $CD4^+$ T cells situated in the tumor core. These pathways encompassed lipid FAS [144].

Emerging evidence underscores the significance of $CD4^+$ T-cell metabolism in modulating its activity and function. Nonetheless, the scarcity of reviews addressing lipid metabolism in lung cancer, which profoundly impacts $CD4^+$ T-cell activity and differentiation, underscores the need for further investigation in this area.

Strategies to enhance immunotherapy by targeting fatty acid metabolism in lung cancer

Targeting specific metabolic pathways in lymphocytes represents a promising therapeutic strategy to advance cancer treatment. Metabolic abnormalities in the TME contribute to immune evasion and resistance to therapy. Thus, interventions aimed at restoring normal lipid homeostasis or selectively inhibiting lipid-related pathways that promote tumor-supportive phenotypes in lymphocytes can enhance the efficacy of cancer immunotherapy (Fig. 3).

Table 1 highlights key metabolic targets, associated drugs, and clinical trials, demonstrating how manipulating these pathways can enhance antitumor immunotherapy and improve immune responses against cancer.

Modulation of lipid uptake and consumption

A promising strategy involves modulating the pathways of lipid uptake and consumption. FA transporters, such as CD36, are crucial for FA uptake in immune cells, particularly in Tregs, in both melanoma and non-small-cell lung carcinoma patients [49]. Targeting CD36 reduces lipid influx in intratumoral Tregs and disrupts the mitochondrial fitness supported by PPAR-β pathways, reprogramming these cells away from an immunosuppressive phenotype [49]. Inhibiting CD36 can alter lipid availability, significantly increasing the tumor infiltration of $CD8^+$ T cells and enhancing the production of antitumor effector cytokines in $CD8^+$ and $CD4^+$ tumor-infiltrating lymphocytes

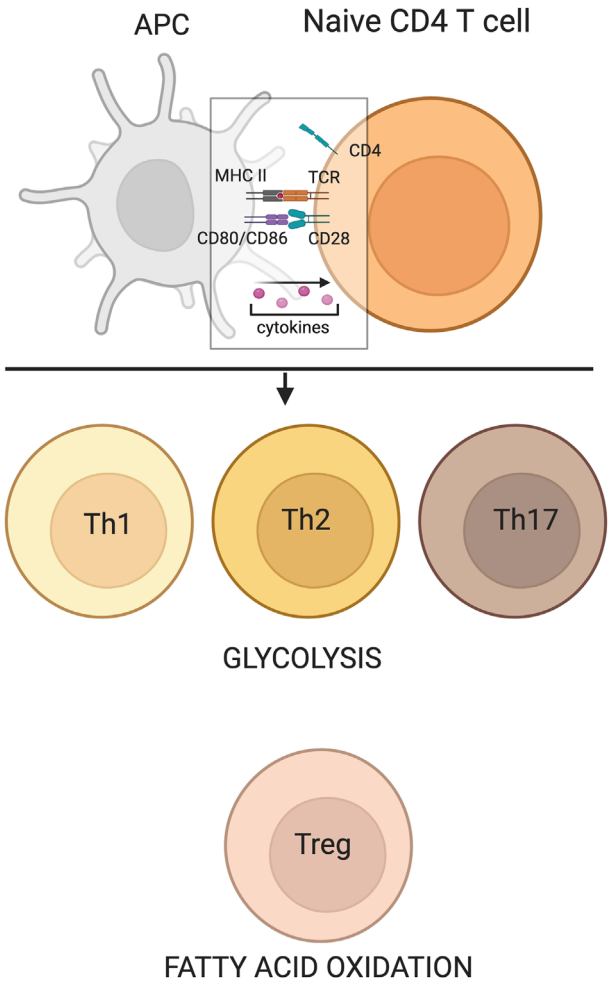

Fig. 2. Fatty acid metabolism in $CD4^+$ T cells. Each subset of $CD4^+$ T cells employs unique metabolic pathways to sustain their respective functions.

(TILs). This approach boosts the antitumor immune response and complements the therapeutic effects of PD-1 blockade [49] (Fig. 3).

The role of ACSL4 in ferroptosis

Liao *et al.* [145] highlighted the pivotal role of Acyl-CoA synthetase long-chain family member 4 (ACSL4) in activating inherent ferroptotic processes through metabolic lipid reprogramming. Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation. This process can be triggered by the activation of ACSL4, leading to the accumulation of oxidized lipids that result in cell death. In the context of cancer, T cells act as immune stress signals, inducing ferroptotic tumor cell death and activating T cells in the TME. The study suggests that the induction of ferroptosis in cancer cells, dependent on ACSL4 activation, challenges the conventional view of CTL-induced tumor apoptosis. The combination of T-cell-derived interferon-gamma (IFN-γ) and arachidonic acid induces a form of immunogenic cell death distinct from the tolerogenic cell death induced by apoptosis. The interplay between ferroptosis and apoptosis presents intriguing possibilities for understanding CTL-killing mechanisms, with implications for cancer immunotherapy, particularly in 'cold' tumors. This strategy synergizes with immune checkpoint blockade (ICB)-triggered IFN-γ signaling to induce and amplify tumor ferroptosis, ultimately leading to significant tumor regression. Targeting arachidonic acid metabolism emerges as a promising approach to enhance the effectiveness of cancer immune checkpoint blockade [145] (Fig. 3).

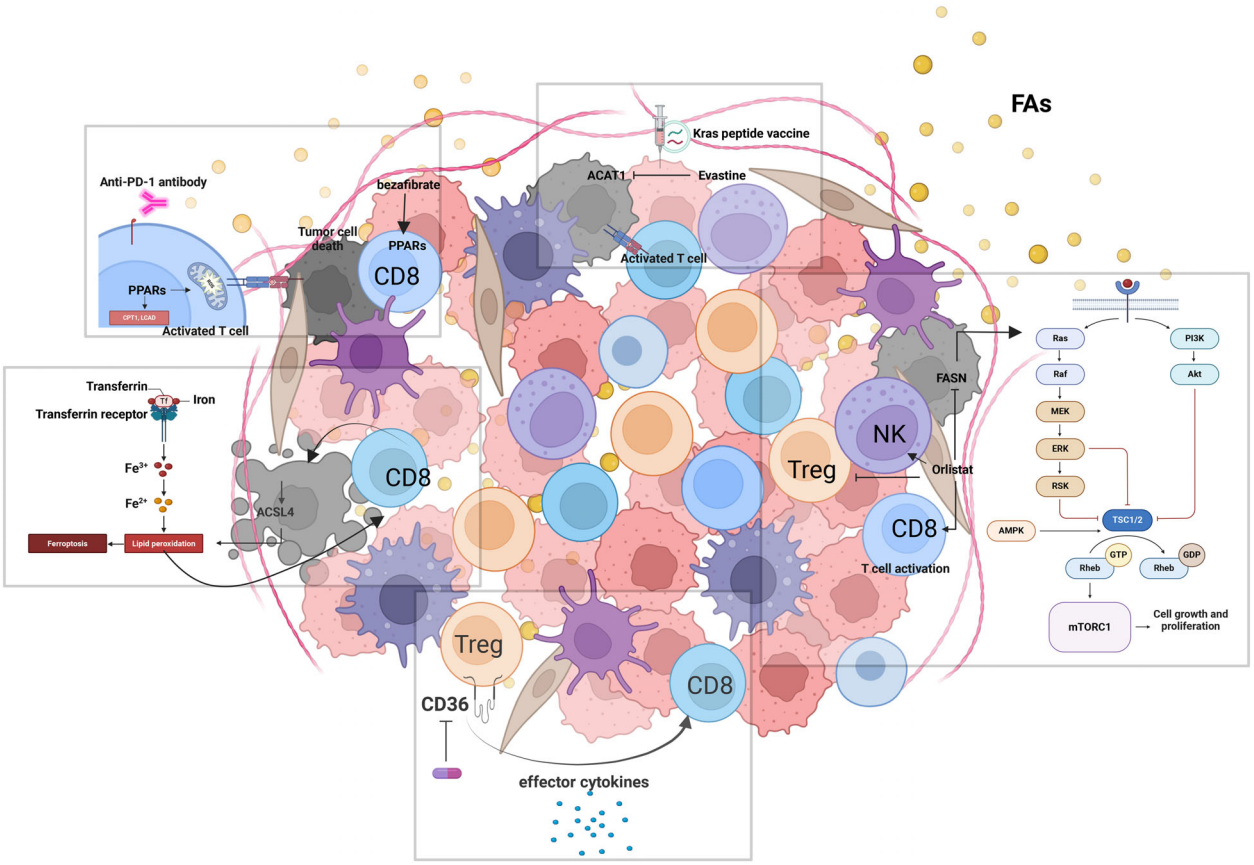

Fig. 3. Strategies to enhance immunotherapy by targeting fatty acid metabolism in lung cancer. Targeting CD36 disrupts lipid influx in intratumoral Tregs, enhancing $CD8^+$ T-cell infiltration and antitumor cytokine production, complementing PD-1 blockade. ACSL4 activates ferroptosis through lipid peroxidation, combining T-cell-derived IFN-γ and arachidonic acid to induce immunogenic cell death and enhance checkpoint blockade efficacy. Inhibiting ACAT1 restores $CD8^+$ T-cell function and reduces lung metastasis, improving immunotherapy outcomes. Combining ACAT-1 inhibitors with Th1-promoting vaccines boosts antitumor immunity. FASN inhibition disrupts glucose metabolism and AKT/ERK pathways, activating NK and $CD8^+$ T cells while reducing Tregs, showing promise in cancer immunotherapy. PPAR activation in $CD8^+$ T cells enhances FAO-related gene expression and ROS production, improving antitumor immunity and the efficacy of checkpoint inhibitors. APC, antigen-presenting cell; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; TME, tumor microenvironment.

ACAT1 and its role in membrane lipid remodeling

Acetyl-CoA Acetyltransferase 1 (ACAT1) plays a crucial role in cholesterol metabolism and the remodeling of membrane lipids [146]. Studies investigating ACAT1's involvement in lung metastasis have revealed a positive correlation between ACAT1 activity and the suppression of $CD8^+$ T-cell function. Inhibition or deletion of ACAT1 has been shown to restore $CD8^+$ T-cell infiltration and activity, thereby reducing lung metastasis and improving the efficacy of immunotherapy [146]. A recent preclinical study explored the therapeutic potential of combining a Th1-promoting Kras peptide vaccine with avasimibe, an ACAT-1 inhibitor, in the context of lung cancer. Results demonstrated that this combinatorial regimen augmented Th1-mediated antitumor immunity, suggesting a promising avenue for further investigation in clinical settings [147]. These findings suggest that targeting cholesterol metabolism through ACAT1 inhibition could help counteract the immunosuppressive phenotype of the TME, thereby enhancing antitumor immune responses (Fig. 3).

FABP5 and its impact on natural killer cells

Fatty acid-binding protein 5 is implicated in tumor progression through its regulation of intracellular lipid homeostasis. Studies in a mouse model of lung cancer metastasis reveal that FABP5 deficiency enhances

Table 1. Summary table of emerging therapeutic strategies targeting lipid metabolism in lymphocytes for cancer treatment.

Metabolic pathway/ target	Drug/trial	Description
Lipid uptake (CD36)	Targeting CD36	Inhibits FA uptake in Tregs, enhances antitumor immunity in melanoma and NSCLC [49]. Complements PD-1 blockade
Ferroptosis (ACSL4)	ACSL4 activation	Induces ferroptotic cell death in cancer cells, enhances immune response [145]
Membrane lipid remodeling (ACAT1)	ACAT1 inhibitors	Inhibits cholesterol metabolism, enhances $CD8^+$ T-cell function, reduces metastasis [146]. Combined with Kras peptide vaccine in lung cancer [147]
FABP5 impact on NK cells	FABP5 targeting	Enhances NK cell activation, reduces lung cancer metastasis [148]
FASN pathway	FASN inhibitors	Inhibits *de novo* lipogenesis, enhances NK and $CD8^+$ T-cell activity, reduces Treg populations [64,149–152]
AMPK pathway	Metformin (NRG-LU001 trial)	Activates AMPK, enhances antitumor immune response [153–155]
PPARs activation	PPAR agonists (bezafibrate)	Upregulates FAO-related genes, enhances $CD8^+$ T-cell function, potentiates anti-PD-1 therapy [156–158,166]
Fish oil supplementation	Clinical Trial (NCT04965129)	Evaluates PUFA n-3 effects on FA metabolism in lung cancer patients undergoing therapy [160,161]
Calorie restriction	FASTIMMUNE study (NCT05703997)	Investigates calorie restriction effects on immune response in extensive-stage SCLC [97,162–165]

susceptibility to metastasis. Mechanistically, FABP5-deficient mice exhibit an accumulation of saturated FA in NK cells, leading to impaired maturation and activation. This effect was not observed in $CD8^+$ T cells, suggesting differential sensitivity to perturbations in lipid metabolism. These findings underscore the intricate relationship between host lipid homeostasis and tumor metastasis, warranting further investigation into the therapeutic potential of targeting FABP5 in cancer [148].

Targeting the FASN pathway

The FASN pathway, essential for *de novo* lipogenesis, represents a compelling therapeutic target due to its frequent overexpression in diverse malignancies, including lung cancer [149]. Dysregulation of FASN within lymphocytes has been implicated in compromised immune responses and the establishment of tumor-promoting phenotypes, notably through the stabilization of PD-L1. Additionally, FASN-mediated FAS is integral to the maturation of immunosuppressive regulatory T cells (Tregs), suggesting that FASN inhibition may hold promise for reprogramming these cells [64]. Recent preclinical investigations have demonstrated the efficacy of FASN inhibitors in mitigating tumor growth and bolstering immune cell function across various cancer models, including lung cancer. Mechanistically, these inhibitors have been shown to disrupt glucose metabolism and the AKT/ERK signaling pathway in cancer cells [150–152]. Notably, the FASN inhibitor orlistat has been observed to activate NK and $CD8^+$ T cells while concurrently decreasing Treg populations, further underscoring the therapeutic potential of targeting FASN within the realm of cancer immunotherapy [152] (Fig. 3).

AMPK pathway as a therapeutic target

The AMP-activated protein kinase (AMPK) pathway is another critical regulator of cellular energy homeostasis, including FA metabolism. Activating AMPK has been proposed as a strategy to counteract the tumor-supportive effects of altered FA metabolism. Preclinical studies have demonstrated that AMPK activation in lymphocytes can suppress tumor growth and improve antitumor immune responses probably by promoting glucose and FA uptake and oxidation [153,154]. Building on promising preclinical results, the NRG-LU001 Phase 2 Randomized Clinical Trial (NCT02186847) was initiated in 2014. This study aims to explore the therapeutic potential of combining metformin, a widely used medication for diabetes, with chemoradiation in patients with unresectable stage IIIA or IIIB NSCLC [155]. Metformin acts by activating AMPK, inhibiting the IGF1-insulin axis, and blocking VEGF. These mechanisms may disrupt cellular growth pathways, downregulate insulin-like growth factors, and inhibit mitochondrial complex I, ultimately leading to the suppression of oxidative phosphorylation and the promotion of immunogenic cell death.

PPARs and SREBPs

Exploring the role of nuclear receptors, such as PPARs, in the context of altered FA metabolism in lymphocytes is gaining attention. PPARs are key regulators of lipid metabolism, and their modulation has been linked to antitumor effects in various cancers [156]. Selective targeting of PPAR isoforms may offer a tailored approach to normalize FA metabolism and promote an antitumor immune response [157]. Notably, pharmacological activation of PPARs with bezafibrate in $CD8^+$ T cells has been demonstrated to augment antitumor immunity through upregulation of FAO-related genes, such as CPT1a and LCAD, and concomitant induction of mitochondrial reactive oxygen species (ROS) production. This metabolic reprogramming toward enhanced FA catabolism not only bolsters $CD8^+$ T-cell effector function but also elicits elevated intracellular ROS levels, particularly within the highly cytotoxic effector T-cell subset [157]. Consequently, this metabolic shift potentiates the therapeutic efficacy of ICIs, such as anti-PD-1 therapy [158], thus highlighting the potential of PPARs agonism as a promising immunotherapeutic strategy (Fig. 3).

Sterol regulatory element-binding proteins (SREBPs) are a family of transcription factors that play a pivotal role in regulating lipid metabolism, including FAS. Upon activation, SREBPs are cleaved and translocate to the nucleus, where they bind to sterol regulatory elements (SREs) in the promoter regions of target genes involved in lipid metabolism [159]. The findings by Kidani *et al.* [125] suggest that targeting SREBPs may represent a novel strategy to enhance antitumor immunity in lung cancer. By modulating SREBP activity, it may be possible to restore $CD8^+$ T-cell function and improve the efficacy of immunotherapy. Further research is needed to fully elucidate the role of SREBPs in $CD8^+$ T-cell regulation and to explore the therapeutic potential of targeting SREBPs in lung cancer.

Ongoing clinical trials

Currently, two promising clinical trials are underway. The first trial (NCT04965129), initiated in 2022, aims to evaluate the impact of fish oil supplementation on lung cancer patients undergoing immunotherapy, chemotherapy, and Tyrosine Kinase Inhibitors while adhering to a high-protein diet. The rationale behind this study is rooted in the potential effects of polyunsaturated FA of the omega-3 class (PUFA n-3), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on specific aspects of FA metabolism. These might include the inhibition of FAS [160] and modulation of PPAR activation [161]. The second trial, the FASTIMMUNE study (NCT05703997), is a Phase 2 interventional clinical trial initiated in 2023. It aims to investigate the efficacy, in terms of a 6-month progression-free survival rate, of a 5-day calorie restriction diet combined with atezolizumab maintenance in patients with extensive-stage small cell lung cancer (ES SCLC). This innovative approach is grounded in preclinical and translational evidence indicating that metabolic interventions, such as calorie restriction, can exploit cancer cell vulnerabilities and potentially augment the efficacy of immunotherapy. Specifically, calorie restriction-induced alterations in leptin signaling pathways might enhance antitumor $CD8^+$ T-cell responses in lung cancer models [108], thereby potentially influencing tumor response to ICIs like atezolizumab [97,162–165].

Future directions and challenges

While targeting lymphocyte metabolism holds great promise for cancer therapy, several challenges remain. The complexity of lipid metabolism necessitates a deeper understanding of the underlying mechanisms to develop effective and targeted therapies. Moreover, the heterogeneity of tumors and individual patient responses poses a significant challenge for clinical translation.

Despite these challenges, the emerging field of lipid metabolism offers a unique opportunity to develop novel therapeutic strategies that can complement existing treatments and overcome resistance mechanisms. By unraveling the intricate relationship between lymphocyte metabolism and tumor progression, we can pave the way for a new era of personalized cancer therapy that harnesses the power of metabolic manipulation to improve patient outcomes.

In summary, targeting lymphocyte metabolism represents a multifaceted approach to cancer therapy, with potential implications for various cancer types. By modulating key enzymes, transporters, and signaling molecules involved in lipid metabolism, we can reprogram immune cells, induce tumor cell death, and restore immune balance within the TME. Continued research in this field promises to unveil novel therapeutic targets and strategies that can significantly impact the lives of cancer patients.

Concluding remarks

Lung cancer, particularly non-small cell lung cancer, has witnessed significant advancements in immunotherapy, notably with ICIs like pembrolizumab, nivolumab, and

atezolizumab. These ICIs have shown remarkable efficacy in subsets of patients with advanced or metastatic NSCLC. The metabolic adaptations of $CD8^+$ and $CD4^+$ T cells within the TME, in response to both the tumor and antitumor therapies, are critical to the success of immunotherapies. In recent years, numerous combination therapies have emerged to enhance the effectiveness of ICIs. These therapies include the use of agonist antibodies, cancer vaccines, and strategies to modulate immune metabolism [167]. When it comes to metabolism, glucose metabolism certainly takes center stage. The role of lipids in cancer has been less studied compared with glucose, largely due to the prominence of the Warburg effect, which identified glucose metabolism as a primary driver of therapeutic resistance for many years. It is only in the past decade that the significance of lipid metabolic pathways in tumor progression has been re-evaluated. Notable progress has since been made in understanding these pathways, particularly in relation to the immune microenvironment and T cells. Emerging evidence suggests that FA metabolism plays a pivotal role in shaping T-cell phenotype, function, and ultimately, antitumor responses. In lung cancer, the dysregulation of FA metabolism profoundly influences $CD8^+$ T-cell behavior, impacting their effector functions, proliferative capacity, and survival within the TME.

For instance, FA metabolism can impact $CD8^+$ lymphocyte activity by modifying membrane composition, which influences receptor clustering and signal transduction [168], or by altering the energy supply necessary for $CD8^+$ T-cell proliferation and effector functions [169]. The abundance of FA also supports regulatory T cells and suppressive myeloid cells, further decreasing the efficacy of $CD8^+$ T cells. Lipid overload induces ER stress, triggering apoptosis in T cells.

Despite this, several points remain to be clarified, such as how TCRs mediate uptake and the pathways lymphocytes utilize internally to change metabolism and generate adaptive responses. Speculatively, lipid metabolism could contribute to CD8 T-cell exhaustion also by influencing epigenetic modifications, such as altering histone acetylation and methylation patterns, which in turn affect the expression of exhaustion-associated genes. Additionally, lipid metabolic pathways may interact with transcription factors or co-factors, such as SREBPs, thereby influencing the activation or repression of crucial transcriptional programs, including the FASN signature [170].

Additionally, it is necessary to understand why FAs induce a stronger response in some contexts while appearing to induce resistance in others.

While the metabolic interplay between FAs and $CD8^+$ T cells in lung cancer is increasingly recognized, the role of FA metabolism in $CD4^+$ T-cell regulation within this context remains largely underexplored. Existing studies are predominantly bioinformatic in nature, highlighting the need for further mechanistic investigations.

Intriguingly, the interplay between metabolism and cancer susceptibility, as well as treatment response, is becoming increasingly evident. For instance, obesity, often associated with dysregulated FA metabolism, is linked to increased cancer risk and poorer treatment outcomes. This highlights the potential of targeting metabolic pathways, including those involving FA, for therapeutic interventions.

Lastly, the role of FAs in other T-cell subpopulations, such as NK and gamma-delta cells, remains largely unexplored. Investigating how this metabolism impacts them is essential, given their close crosstalk with other T-cell populations, both under basal conditions and in the context of therapy.

Given the shared reliance of both cancer cells and T cells on FA oxidation, future research should focus on understanding the potential for metabolic competition within the TME. Deciphering the intricate relationship between FA metabolism and T-cell function in lung cancer could unveil novel therapeutic targets to enhance antitumor immunity and ultimately improve patient outcomes.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

GC, JP, LA, and AM wrote the manuscript.

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