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REVIEW

Precise targeting of lipid metabolism in the era of immuno-oncology and the latest advances in nano-based drug delivery systems for cancer therapy

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Abstract Over the past decade, research has increasingly identified unique dysregulations in lipid metabolism within the tumor microenvironment (TME). Lipids, diverse biomolecules, not only constitute biological membranes but also function as signaling molecules and energy sources. Enhanced synthesis or uptake of lipids in the TME significantly promotes tumorigenesis and proliferation. Moreover, lipids secreted into the TME influence tumor-resident immune cells (TRICs), thereby aiding tumor survival against chemotherapy and immunotherapy. This review aims to highlight recent advancements in understanding lipid metabolism in both tumor cells and TRICs, with a particular emphasis on exogenous lipid uptake and endogenous lipid *de novo* synthesis. Targeting lipid metabolism for intervention in anticancer therapies offers a promising therapeutic avenue for cancer treatment. Nano-drug delivery systems (NDDSs) have emerged as a means to maximize anti-tumor effects by rewiring tumor metabolism. This review provides a comprehensive overview of recent literature on the development of NDDSs targeting tumor lipid metabolism, particularly in the context of tumor immunotherapy. It covers four key aspects: reprogramming lipid uptake, reprogramming lipolysis, reshaping fatty acid oxidation (FAO), and reshuffling lipid composition on the cell membrane. The review concludes with a discussion of future prospects and challenges in this burgeoning field of research.

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1. Introduction

Cancer is currently the 2nd leading cause of death worldwide and is projected to become the top killer by 2060[1,2]. Altered cellular metabolism and energetics are recognized as hallmarks of malignant cancer cells, fueling their uncontrolled growth and maintenance[3,4]. In the 1920s, Otto Warburg identified a peculiar phenomenon that liver cancer cells utilize glycolysis to produce adenosine triphosphate (ATP), lipids, and amino acids for energy supply in unconventional ways[5]. Glucose serves as a crucial input for major anabolic pathways. However, tumor cells increase their demand for local nutrients and oxygen, leading to the creation of an acidic, hypoxic, and glucose-depleted tumor microenvironment (TME). Malignant tumor cells are forced to autonomously alter their flux through continuously adjusting their metabolic profile to adapt to the elevated bioenergetics and biosynthetic needs.

Lipid metabolism and the malignant phenotype of tumors are highly intertwined. Lipids, diverse compounds like fatty acids (FAs), phospholipids (PLs), cholesterol (Chol), and signaling molecules, including bioactive lipids such as prostaglandin E2 (PGE2) and lysophosphatidic acid (LPA), play vital roles in signaling and energy supply within the TME, influencing tumorigenesis and dissemination[6,7]. Tumor cells increase *de novo* lipogenesis (DNL), lipid storage, and lipid uptake to support energy production and proliferation, essential for invasion and metastasis[6,8–10]. Lipids also maintain cellular membrane structure and signaling pathways crucial for cancer cell growth and migration[11–15]. Understanding lipid metabolism's role in cell survival mechanisms distinguishes cancer cells from normal cells and offers potential therapy targets. This review summarizes recent advances in lipid impact on cancer progression, focusing on exogenous lipid uptake and endogenous lipid synthesis in tumor cells.

Anomalous lipid metabolism also significantly influences the immune-related response of tumor cells to adapt to the TME. It plays a crucial role in modulating the quantity, activation, and function of immune cells, including cytotoxic $CD8^+$ T cells, natural killer (NK) cells, tumor-associated macrophages (TAMs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs)[16]. In theory, lipids serve as a source of energy for tumor-resident immune cells (TRICs) and provide precursors for bioactive lipids and components of cellular membranes. However, contradictory findings suggest that alterations in the levels of specific lipid species can affect the function of cytotoxic immune cells, potentially weakening the effectiveness of immunotherapy[17]. Therefore, gaining a comprehensive understanding of the dual role of lipid metabolism in the immune-related tumor response is crucial for elucidating the landscape of tumor immunology and designing tailored immunotherapies. In this discussion, we will focus on exploring the dysregulated lipid metabolism in TRICs, including its effects on their function and phenotype.

Targeting lipid metabolism for cancer therapy is an attractive strategy. The current strategy focuses on key proteins involved in exogenous lipid uptake, lipolysis, fatty acid oxidation (FAO), and lipid synthesis. Due to the complex composition of lipids, various immune cells respond differently to alterations in lipid metabolism. Therefore, further clinical applications should consider precise targeting of lipid metabolism to maximize anti-tumor efficacy. Nanotechnology has led to the development of the nano-drug delivery systems (NDDSs), which utilizes functional nanocarriers for targeted drug delivery[18–20]. NDDSs, with its unique physical and chemical properties, can be easily internalized by specific immune cells and re-educate the TME to strengthen the immune response. This approach is emerging as a frontier in cancer chemo-immunotherapy[21–24]. In conclusion, we summarize innovative strategies for precisely targeting lipid metabolism using NDDSs. This provides a basis for developing potential combined therapies, especially immunotherapy.

2. Lipid metabolism-mediated the cancer-immune crosstalk

The lipid metabolism pathway has gained considerable attention recently for its crucial role as a metabolic hallmark of tumor cells. Tumor cells primarily produce large amounts of lipids by over-activating endogenous lipid synthesis pathways or by utilizing exogenous pathways for lipid uptake to support their accelerated proliferation and metastasis. Additionally, the lipid metabolism of immune cells is often reprogrammed within the TME, further facilitating tumor immune evasion.

2.1. Direct impacts of lipid metabolism on malignant cancer cells

2.1.1. De novo synthesis of endogenous lipids

Enhanced DNL is a common metabolic aberration observed in tumor cells[25–27]. Tumor cells exhibit heightened synthesis of lipids to maintain lipid homeostasis, fulfilling the demands for proliferation and growth (Fig. 1)[6,16,28]. The DNL pathway begins with citrate generated in the mitochondrial tricarboxylic acid (TCA) cycle, which is then converted to acetyl-CoA (Ac-CoA) in the cytosol by ATP-citrate lyase (ACLY). Key molecular components include Ac-CoA carboxylases (ACCs) 1 and 2, responsible for producing malonyl-CoA in the rate-limiting step of lipogenesis. Subsequently, fatty acid synthase (FASN) synthesizes palmitate (PA, 16:0), the initial product of FA synthesis, by utilizing Ac-CoA and malonyl-CoA. PA, a saturated FA, can be further converted to monounsaturated fatty acid palmitoleate (palmitoleic acid) through desaturation by stearoyl-CoA desaturase (SCD) and FA desaturase 2 (FADS2). Additionally, elongation of very long-chain fatty acid proteins (ELOVL enzymes) elongates PA. Alternatively, cells can incorporate essential FAs to generate polyunsaturated fatty acids (PUFAs) like linolenic acid (LA) and α-linolenic acid (ALA). Synthesized lipids are stored as triacylglycerol (TAGs) in lipid droplets (LDs), with diglyceride acyltransferases (DGATs) catalyzing the synthesis of TAGs from diacylglycerol (DAG). Other lipid classes, such as PLs, consist of two FA chains attached to a glycerol backbone.

Chol is a vital lipid synthesized *de novo*, crucial for membrane structure and fluidity. Its production occurs in the endoplasmic reticulum (ER) through the mevalonate pathway, involving a complex mechanism. Ac-CoA initiates Chol production, with

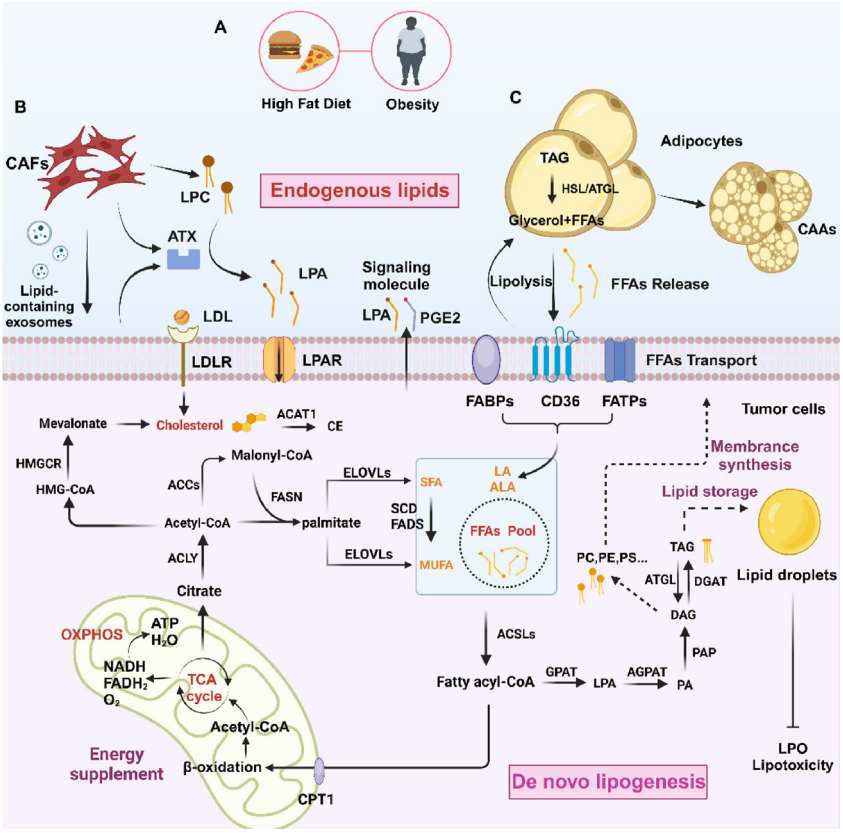

Figure 1 Lipid metabolism reprogramming in tumor cells. Tumor cells generate substantial amounts of lipids by over-activation the lipid *de novo* synthesis pathways or exogenous lipid uptake pathways (A−C) to support their increased proliferation and metastasis. Figures generated with BioRender (https://biorender.com/).

HMG-CoA reductase (HMGCR) serving as the rate-limiting enzyme, yielding mevalonate in Chol synthesis (Fig. 1)[29−31]. Additionally, sterol regulatory element binding proteins (SREBPs), particularly SREBP-2, also act as transcription factors pivotal in regulating Chol biosynthesis[32−34]. Overall, the DNL pathway involves enzymes such as ACLY, ACCs, FASN, SCD, DGATs, HMGCR and SREBPs.

Naturally, the upregulation of DNL is a well-known phenomenon that is induced by the elevation of various lipogenic enzymes in tumor cells. One example is the ACLY enzyme, which is highly up-regulated in various types of cancer and supports proliferation, migration, adhesion and stemness maintenance. As a result, ACLY has recently attracted considerable interest as a potential therapeutic anti-tumor target[35−38]. Interestingly, the role of ACLY inhibition in tumor immunity and immunotherapy efficacy also cannot be ignored[39,40]. Inhibition of ACLY overcomes immunotherapy resistance by PUFA peroxidation and cGAS-STING activation in hepatocellular carcinoma (HCC)[41]. Equally noteworthy is that, FASN-mediated DNL induction in cervical cancer cells is correlated with lymph node metastasis and can promote migration and invasion *in vitro*[42]. The aggressiveness of intrahepatic cholangiocarcinoma is also correlated with the upregulation of FASN[43]. Furthermore, extensive research underscores Chol's pivotal role in governing cancer proliferation and immune evasion[31,44,45]. In melanoma, the unfolded protein response component X-box binding protein 1 (XBP1) promotes Chol synthesis and secretion *via* tumor-derived exosomes (Exo), activating MDSCs and inducing immunosuppression[46]. Notably, simvastatin, a Chol biosynthesis inhibitor, exhibits the potential to bolster antitumor immunity in colorectal cancer (CRC)[47]. Moreover, the substantial enrichment of the Chol gene profile in non-small cell lung cancer (NSCLC) underscores the therapeutic potential of statins in combination with immune checkpoint blockade (ICB), offering improved therapeutic efficacy[48]. Thus, adaptive metabolic plasticity of DNL in tumor cells demonstrate the prominent role in lipid metabolic reprogramming.

2.1.2. *The supply and uptake of exogenous lipid for tumor cells*

2.1.2.1. *The main sources of exogenous lipid*

(1) Adipocytes and Stromal Cells: An important lipid metabolism abnormality marker of cancer cells that has come under intense observation relates to the ability of these cells to uptake exogenous lipid from circulation or within the microenvironment and may be exacerbated in obesity (Fig. 1). The extracellular release of the free fatty acids (FFAs) is mostly from cancer associated adipocytes (CAAs) and tumor-fat tissue after lipolysis induced by tumor secretions to transfer and store in LDs of tumor cells, as the emerging supporters in cancer[49−52]. Especially breast cancer (BC) is the major area of study for the impact of exogenous lipids on tumor progression and poor patient prognosis given the containing or adjacent to the largest swaths of adipocytes in mammary fat pad[53,54].

In addition to adipocytes providing exogenous lipids for tumor cells, a recent study showed that CRC can absorb lipids metabolites shed

by cancer-associated fibroblasts (CAFs) to increase migration, which are the most abundant stromal cells within the TME. Specifically, CAFs undertake lipidomic reprogramming and enrich for FAs and PLs. *In vitro*, the migration of CRC cells induced by CAFs is eliminated by either reducing the uptake of FAs or knocking down FASN[55]. Similarly, pancreatic ductal adenocarcinoma (PDAC) could induce tissue-resident pancreatic stellate cells into activated CAFs by autotaxin-LPA axis to promote PDAC cell proliferation[56]. In addition, CAFs can use Exo to deliver large amounts of lipids to cancer cells in order to increase growth[57].

(2) Dietary factors: Moreover, dietary lipid sources, particularly exposure to high-fat diets (HFDs) and obesity, can interact with cancer initiation and growth through various mechanisms, facilitated by cancer cells acquiring abundant exogenous lipids (Fig. 1)[16,58]. For instance, in the models of colorectal adenocarcinoma, BC, and melanoma, HFDs have been demonstrated to accelerate carcinogenesis and tumor development *in vivo* by reprogramming fat utilization within the TME[59]. In another research, HFDs could enhance intestinal stemness and tumorigenicity through a PPARα/δ-FAO pathway[60]. Additionally, peritoneum-derived adipocytes resulting from HFDs induce significant LDs accumulation and FAO in gastric cancer (GC) cells through the transcriptional upregulation of DGAT2 in a C/EBPα-dependent manner, thereby promoting peritoneal metastasis of GC[61]. A study of 2.6 million Catalan individuals aged 40 and above found that higher obesity duration and degree in young adulthood, and earlier high BMI onset, increase the risk of 18 cancer types[62]. Also, hypercholesterolemia and dyslipidemia are also linked to elevated risk of BC and poor prognosis in patients[63]. These findings suggest that in lipid-enriched environments caused by HFDs, cancer cells may enhance lipid uptake to facilitate cell growth mechanisms.

2.1.2.2. The main proteins related to exogenous lipid. CD36 is a membrane-bound glycoprotein and scavenger that has been recognized as an essential mediator of lipid-driven cell adaptation for tumor survival, participating in the transport of exogenous lipids into the cytoplasm[64,65] A recent study showed that co-culturing human adipocytes and BC cells increased CD36 expression, promoting FAs import into BC cells and STAT3 signaling pathways activation to drive tumor progression[66]. Furthermore, CD36 upregulation in oral squamous cell carcinoma stimulates metastasis, and treatment with the anti-CD36 drug inhibits lymph node and lung metastasis or even complete remission[67]. Latest work shows that CD36 initiates Src signaling to facilitate lung adenocarcinoma cell propagation and actin rearrangement associated with metastasis under HFDs[68].

Fatty acid transport proteins (FATPs) are a large number of proteins involved in FAs uptake and play the decisive role in long-chain fatty acids (LCFAs) transport. Humans have 6 highly related FATPs proteins, that are primarily localized to the intracellular and cellular membranes[69]. They have shown increased expression in most cancers. For example, multiple myeloma (MM) cells could trigger lipolysis of adipocytes in bone marrow (BM). The FFAs that are released are absorbed by MM cells *via* FATP1 and FATP4, causing growth or lipotoxicity[70]. Similarly, FATP1, which is aberrantly expressed in melanoma, takes up adipocyte-derived lipids. Inhibition of FATPs specifically reduces melanoma lipid uptake, invasiveness and progression[71].

Fatty acid binding proteins (FABPs), in particular FABP4, are another key lipid protein involved in the delivery of FAs to cancer cells. FABP4 is typically located in the cytoplasm and is associated with the intracellular transport of FAs among organelles, but can also be secreted[72]. In BC cells, exogenous FABP4 can trigger the expression of CD36 and FABP5[66]. In CRC, miR-211 targets FABP4 to inhibit cell migration, invasion, and the EMT process[73]. As such, FABPs profiling may also provide a mechanism for recognizing the growth and aggressiveness of multiple cancers.

Cells primarily acquire exogenous Chol through receptor-mediated uptake mechanisms, primarily involving low-density lipoprotein (LDL) bound to the low-density lipoprotein receptor (LDLR) and high-density lipoprotein (HDL) bound to scavenger receptor class B type 1 (SR-B1)[44]. These pathways collectively regulate cellular Chol levels. Specifically, research has revealed that LDLR-mediated Chol uptake restrains membrane lipid peroxidation (LPO) and reduces tumor susceptibility to ferroptosis in melanoma[74]. However, in HCC, downregulation of LDLR leads to activation of the MEK/ERK pathway, thereby partially contributing to *de novo* Chol synthesis, which serves as a major driver of the oncogenic phenotype[75].

In summarizing, there is much evidence that the provision of exogenous lipids to tumor cells is a common phenotype, in which multiple mechanisms are involved in supporting proliferation and metastasis (Fig. 1).

2.2. *Lipid metabolism-mediated tumor-resident immune cells*

Given the intricate metabolic diversity and differentiation stages of immune cells, accumulating data underscore the pivotal role of lipid metabolism impairments in orchestrating immunosuppression and tumor immune evasion. Specifically, TRICs exhibit metabolic adaptations characterized by enhanced lipid uptake or storage, which correlates with their functional impairment. Thus, in this section, we delineate immune cells into tumor-promoting and tumor-suppressive phenotypes to elucidate how their metabolic profiles and lipid utilization mechanisms modulate their functions within the TME (Fig. 2).

2.2.1. *Alteration of lipid metabolism on immune promoting cells activation, differentiation and function*

2.2.1.1. $CD8^+$ cytotoxic T cells. Cytolytic effector cells, notably tumor-infiltrating $CD8^+$ cytotoxic T cells, play a pivotal role in eliminating pathogens through cytokine and granzyme secretion, as well as direct killing of cancer cells[76–78] However, within the TME, $CD8^+$ cytotoxic T cells often exhibit dysfunction due to the immunosuppressive milieu. Metabolism serves as a driving force dictating the extent and nature of $CD8^+$ cytotoxic T cells activation, differentiation, function, and fate[79]. Notably, a common metabolic alteration observed in the TME is lipid accumulation, which is associated with $CD8^+$ cytotoxic T cells dysfunction[80]. In this section, we summarize the relationship between lipid-induced immunosuppressive TME and $CD8^+$ cytotoxic T cells functionality.

Accumulating evidence suggests that elevated lipid levels in dysfunctional tumor-infiltrating $CD8^+$ T cells may result from an enhanced DNL or lipid input[81]. Transcription factors including SREBPs, control lipid synthesis by upregulating ACLY[82,83]. Inhibition of ACLY has been shown to reduce interferon γ (IFNγ) production and proliferation in activated T cells, indicating its significance in $CD8^+$ T cells function[84–86]. In addition, in the light of PPAR-induced differentiation of naïve to effector T cells,

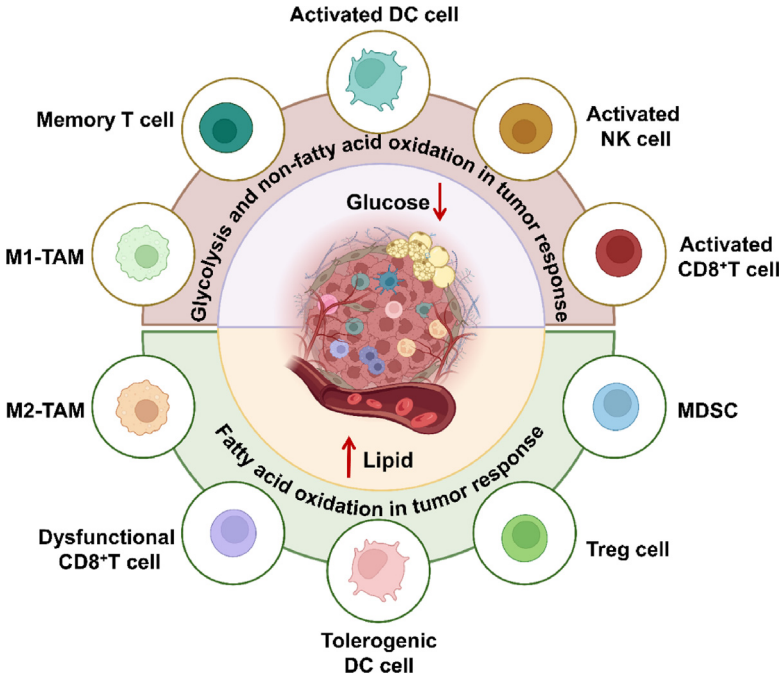

Figure 2 The metabolic phenotypes of tumor-resident immune cells in the TME. The TME is characterized by low glucose and high lipid levels, which sustain lipid-dependent metabolic programs in tumor-resident immune cells, which were associated with tumor-promoting and tumor-suppressive phenotypes. Figures generated with BioRender (https://biorender.com/).

upregulates FAO and increased numbers of functional effector T cells, there is an opportunity for combination therapy that can reprogram of energy metabolism through PPAR signaling in T cells with ICB therapy[87].

Moreover, ACC, a key enzyme in FA biosynthesis, regulates the proliferation and survival of $CD8^+$ cytotoxic T cells in mice[88]. However, Chol deficiency induces autophagy-mediated apoptosis of T cells by SREBP2/LXR alterations, especially in tumor-infiltrating $CD8^+$ T cells[89].

In addition to DNL, tumor-infiltrating $CD8^+$ T cells adapt to the increased lipid abundance within the TME by upregulating the expression of CD36[90], facilitating the intracellular accumulation of oxidized low-density lipoprotein (OxLDL), and inducing functional exhaustion mediated by LPO and p38 phosphorylation. Ablation of CD36 suppresses LPO, enhancing the anti-tumor functions of $CD8^+$ T cells. Furthermore, CD36 mediates the uptake of FAs, especially arachidonic acid (AA), in tumor-infiltrating $CD8^+$ T cells, leading to LPO and ferroptosis[91]. Inhibiting CD36 or ferroptosis effectively restores the anti-tumor activity of $CD8^+$ T cells, particularly in combination with PD-1 antibody (Ab) therapy. In patients and mouse models of PDAC, tumor-infiltrating $CD8^+$ T cells progressively enrich specific LCFAs through downregulation of very-long-chain acyl-CoA dehydrogenase (VLCAD), impairing mitochondrial function and reducing FA catabolism[92]. However, among LCFAs, linoleic acid (LA; C18:2n-6) in $CD8^+$ T cells was significantly lower on activation, suggesting that it might be a major positive regulator during T cell activation[93]. Other lipid species, Chol in the TME could induce $CD8^+$ T cells expression of immune checkpoints and exhaustion by increasing ER stress sensor XBP1 after homing to the tumor bed[80]. Tumor-derived PGE2 restricts the proliferative proliferation and effector differentiation of $TCF1^+$ stem-like $CD8^+$ T cells within tumors, thereby facilitating cancer immune escape[94].

Furthermore, obesity has been linked to functionally exhausted $CD8^+$ T cells in various mouse models of cancer[59]. Interestingly, tumor cells, but not $CD8^+$ T cells, respond dynamically to obesity by downregulating prolyl hydroxylase-3 (PHD3) expression, resulting in altered FFAs mobilization. This shift in fuel partitioning leads to T cell dysfunction, suppressing anti-tumor immunity within the obese TME. Similarly, in obesity-associated BC, adipocyte-driven leptin/STAT3 or PD-1/STAT3 pathway promotes FAO and reduces glycolysis in $CD8^+$ T cells, inhibiting effector functions and facilitating tumor growth[95].

Overall, recent studies suggest that the abnormal lipid metabolic landscape endows tumor-infiltrating $CD8^+$ T cells with unique metabolic flexibility, presenting a novel avenue to combat tumor progression (Fig. 3). A deeper understanding of these mechanisms will promote the survival of cytotoxic T cells in the metabolically hostile TME, thereby enhancing cancer immunotherapy efficacy.

2.2.1.2. NK cells. NK cells are fundamental elements of the innate immune system The intricate interplay between lipid metabolism and NK cells dysfunction, particularly within tumor-infiltrating NK cells (TINK), carries significant clinical implications. Notably, in aggressive B-cell lymphoma, compromised NK cells functionality is correlated with the lipid-rich microenvironment of the lymphoma (Fig. 3). Transcriptomic analyses have shed light on the involvement of peroxisome PPARγ, FABPs, and CD36 in modulating NK cells lipid metabolism within this context[96].

Moreover, in the setting of obesity, the lipid-enriched TME prompts TINK to uptake exogenous lipids, consequently activating the PPARα/δ pathways. This activation hampers the secretion of lytic granules containing perforin and granzymes, thus compromising the antitumor functions of NK cells-a

phenomenon termed "cellular metabolic paralysis"[97]. Restoration of NK cells' cytotoxicity requires reversal of this metabolic paralysis, which can be achieved by inhibiting PPARα/δ or by preventing lipid transport into the mitochondria. Furthermore, NK cells isolated from surgically treated mice and human CRC patients exhibit heightened lipid accumulation, attributed to the upregulation of scavenger receptor class A member 1 (MSR1), CD36, and CD68. This elevation in lipid content correlates with reduced efficacy in targeting tumors *ex vivo*, suggesting a potential adverse impact of post-surgical lipid supply on the anti-tumor immune response and metastasis formation[98]. Tumor-derived PGE2 impairs NK cells-type 1 conventional DCs (cDC1) axis resulting in cancer immune evasion[99]. In summary, lipid metabolic reprogramming intricately orchestrates receptor signaling events, ultimately shaping the fate of NK cells within the TME.

2.2.1.3. DCs. DCs are the specialized antigen-presenting cells (APC) that give full play to bridge innate and adaptive immune systems that trigger the activation of cytotoxic T cells It is being increasingly acknowledged that lipid metabolic traits of tumor-infiltrating DCs (TIDCs) may be inextricably linked to immunosuppressive phenotypes[100]. DNL facilitates the expansion of membranes of the ER and Golgi, which is required for DCs activation and maturation[101]. Paradoxically, over-activated DNL will eventually result in excessive lipids in the cytoplasm to reduce the expression of major histocompatibility complex class I (MHC I) and costimulatory factors in DCs, impairing antigen-presenting function (Fig. 3). Accordingly, TOFA (ACC inhibitor) or C75 (FASN inhibitor) could enhance antigen processing by elevating the ER stress of DCs[102].

In addition to DNL, the uptake of lipids from the environment is one of the major approaches to maintaining the intracellular lipid pool in DCs. The types of saturated or unsaturated lipids are particularly crucial for DCs (Fig. 3). *In vitro* culture systems, saturated fatty acids (SFA) can activate the expression of costimulatory ligands and cytokine production in bone marrow-derived DCs (BMDCs)[103]. In contrast to SFA, the PUFA has been shown to inhibit LPS-induced DCs maturation. Interestingly, TIDCs exhibit a "lacy" phenotype featuring highly enriched LDs, and display an impaired potential to present tumor-associated antigens[104]. In agreement with these findings, the engulfment of FA-carrying tumor-derived Exo by TIDCs could upregulate the expression of PPAR*a* and activate FAO to induce immune dysfunction. Importantly, the PPAR*a* inhibitor GW6471 effectively corrected the immune dysfunction of TIDCs to strongly increase the number and function of tumor antigen-specific $CD8^+$ T cells and enhanced the anti-tumor efficacy of PD-1 Ab in MC38-OT1-bearing mice[105]. Moreover, tumor-derived PGE2 programs mouse and human cDC dysfunction, which fails to orchestrate anti-cancer $CD8^+$ T cells response in preclinical mouse cancer models of melanoma[106].

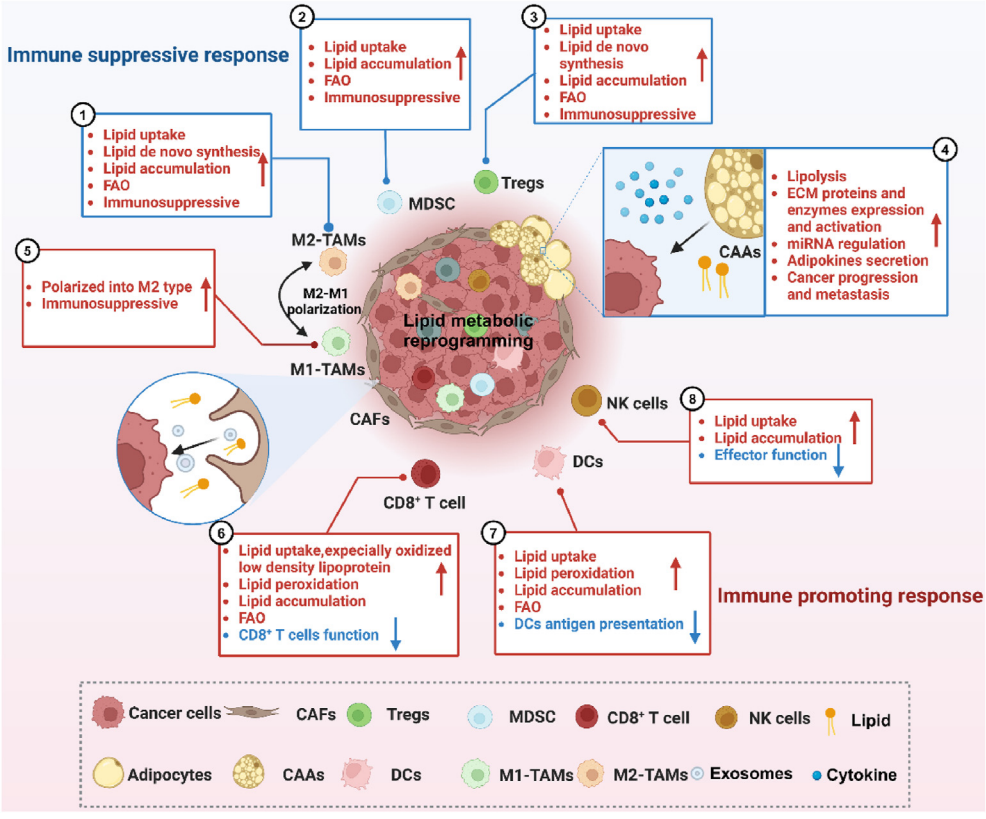

Figure 3 Lipids and metabolic pathways with an impact on the immune response and tumor development. Impaired lipid metabolism is a crucial factor in coordinating immunosuppression and tumor immune evasion. For instance, tumor-infiltrating $CD8^+$ T cells and NK cells exhibit increased lipid uptake, lipid accumulation and FAO. Besides, CAAs are activated by tumor cells leading to increased lipolysis. The accumulation of lipids in TAMs also modulates their polarization and functional phenotypes to M2. Immunosuppressive cells, such as Tregs and MDSCs, display increased lipid uptake and FAO, further augmenting their potent immunosuppressive capabilities. Figures generated with BioRender (https://biorender.com/).

2.2.2. *Alteration of lipid metabolism confer the function of immune suppressive cells*

2.2.2.1. Tumor associated macrophages. TAMs are pivotal immune cells that play a critical function in immune responses and exhibit a variety of phenotypes Two opposing states of TAMs polarization have been conventionally characterized: the pro-inflammatory, tumor-suppressing M1 state and the pro-growth, tumor-promoting M2 state[107]. Generally, M1-TAMs are predominantly dependent on glycolysis and present with impaired TCA cycle and mitochondrial oxidative phosphorylation (OXPHOS). In contrast, lipid uptake, lipid accumulation and FAO are essential for the full activation of M2-TAMs[108,109].

Notably, M2-TAMs isolated from both murine and patient's tumor tissues are lipid-enriched as a result of elevated lipid uptake[110]. The classical activation of M2-TAMs is driven by IL-4/IL-10 signaling, which leads to increased expression of genes regulating FAO and mitochondrial biogenesis, such as CD36[110], carnitine palmitoyltransferase 1 (CPT1), and peroxisome proliferator-activated receptor gamma coactivator 1beta (PGC1β). Additional, the abnormal Chol metabolism also manipulates macrophage fate. In HCC, TAMs are induced to overexpress the Chol oxidase CH25H, leading to the accumulation of 25-hydroxycholesterol (25-HC) to promote their immunosuppressive phenotype. Targeting CH25H may improve the antitumor effect of anti-PD-1 therapy[111].

Additionally, DNL is activated in response to M2-TAMs polarization, in which SREBP1 plays a crucial role[112]. Regarding lipid uptake, CD36 is upregulated in metastasis-associated macrophages (MAMs), leading to increased LDs formation and the engulfment of extracellular vesicles containing LCFAs. This drives the functional reprogramming of macrophages in liver metastasis[113]. Blocking CD36 in MAMs restores liver $CD8^+$ T cell immunity and attenuates liver metastasis in mouse models.

Moreover, in recurrent glioblastoma (GBM) patients with a poor prognosis, Ac-CoA from FAO upregulates CD47 transcription and impairs TAMs immune function. Combining FAO blockade with etomoxir (ET) and anti-CD47 Ab treatment impairs tumor growth and enhances macrophage phagocytosis[114]. In conclusion, the immune phenotypes of TAMs are particularly vulnerable to changes in lipid metabolism, highlighting the potential therapeutic opportunities for targeting lipid metabolic pathways in the TME (Fig. 3).

2.2.2.2. MDSCs. MDSCs constitute a heterogeneous population of immature myeloid cells renowned for their potent immunosuppressive properties[115,116] Analogous to M2-TAMs, intra-tumoral MDSCs within the TME exhibit enhanced FAO and upregulation of lipid uptake receptors, such as CD36, MSR1, and FATP1/6, facilitating the accumulation of lipids from the TME[117–120]. This lipid-rich milieu enhances the immunosuppressive capabilities of MDSCs, particularly targeting $CD8^+$ T cells. Inhibition of FAO using ET has been demonstrated to diminish the immunosuppressive function of MDSCs, synergizing with other therapeutic modalities to effectively suppress tumor growth, especially in models of lung and colon carcinoma[121]. Moreover, MDSCs with heightened expression of FATP2, a fatty acid transport protein, induce T cell exhaustion through the production of reactive oxygen species (ROS). Blocking FATP2-mediated lipid accumulation alleviates MDSCs-induced T cell exhaustion and enhances the anti-tumor efficacy of anti-PD-L1 therapy in preclinical tumor models[119].

In another study, Chol accumulation inhibits the Arginase-1 (Arg1) expression in MDSCs to blunt tumor immunosuppression. Mechanically, receptor-interacting protein kinase 3 (RIPK3), which activates Chol synthesis *via* AKT-mTORC1-SREBP2-HMGCR pathway, is deficient in tumor-infiltrating MDSCs. Therefore, downregulating RIPK3 by Itraconazole could enhance immunosuppressive activity of MDSCs and worsen CRC tumor growth[122]. Furthermore, MDSCs exposed to unsaturated FAs upregulate DGAT1, a key enzyme involved in FA uptake and triglyceride synthesis[123]. Targeting DGAT1 in MDSCs cultured with tumor explanted supernatant and unsaturated FAs diminished lipid accumulation and their suppressive function on $CD8^+$ T cells. Remarkably, DGAT1 inhibition provided additional therapeutic benefits for ICB, thereby delaying B16-F10 and LLC tumor growth. In summary, the abundant FAs in TME not only as metabolic fuels, but also as critical signaling molecules modulate the activation of MDSCs (Fig. 3).

2.2.2.3. Tregs. Tregs possess unique immune and metabolic characteristics, regulating immune responses and facilitating tumor immune evasion[124] Unlike cytotoxic $CD8^+$ T cells, $Foxp3^+$ Tregs rely more on FAO than glycolysis for energy[125]. Alterations in lipid metabolism are central to Tregs activation, with pharmacological inhibition of CPT1 restraining Tregs proliferation[126]. Intra-tumoral Tregs exhibit enhanced lipid metabolism through activating CD36-PPARβ signal to fine-tune mitochondrial function, compared to peripheral Tregs in melanoma, NSCLC, and MC38 colon cancer[127]. Genetic deletion of CD36 in Tregs suppresses tumor growth, reduces intra-tumoral Tregs, enhances cytotoxic $CD8^+$ T cell activity, and synergizes with anti-PD-1 therapy without disrupting immune homeostasis (Fig. 3).

These findings underscore the importance of lipid-derived signaling molecules in tumor and immune cell viability and function within the TME. Targeting the altered lipid metabolism of both tumor and TRICs represents a promising immunometabolic checkpoint for improving immunotherapy outcomes.

3. Targeting lipid metabolism combined with tumor immunotherapy

Malignant cells, particularly those with high aggressiveness, exhibit a pronounced propensity for lipid accumulation and utilization, prompting exploration into targeting lipid metabolism alongside immunotherapy for cancer treatment. This section delineates the landscape of inhibitors and agonists modulating lipid metabolism and drawing insights from preclinical investigations and ongoing clinical trials.

Inhibiting lipid uptake has emerged as a promising therapeutic avenue in oncology. For instance, in HCC, the CD36 inhibitor SSO demonstrates potential in synergizing with anti-PD-1 Ab by reinstating $CD8^+$ T cell responses while suppressing Tregs and MDSCs[128]. Concerning lipid synthesis, inhibition of FASN by compounds like orlistat and ASC40 yields efficacy in impeding tumor growth by curtailing palmitoylation of MHC I, particularly efficacious when coupled with anti-PD-L1 Ab[129]. Notably, the ASC40 tablet is undergoing Phase III trials in combination with bevacizumab for recurrent GBM (NCT05118776).

PPARs, which encompass a family of lipid-activated nuclear receptors including PPARα, PPARβ/δ, and PPARγ, serve as key lipid sensors regulating systemic energy metabolism and influencing immune responses within the TME[130]. Recent investigations unveil tumor cells' evasion of immune checkpoint targeting *via* the PPARγ/VEGF-A axis, fostering MDSC expansion and $CD8^+$ T cell dysfunction. Administration of a PPARγ antagonist in orthotropic and spontaneous HCC tumor-bearing

murine models induces a TME shift from immunosuppressive to stimulatory, reinstating tumor sensitivity to anti-PD-L1 therapy[131]. Intriguingly, clinical trials evaluate the efficacy of anti-PD-1 combined with rosiglitazone, a PPARγ agonist, to counteract tumor hypoxia and immune dysfunction (NCT04114136).

PGE2, a potent immunoregulatory lipid generated by cancer cells *via* aberrant cyclooxygenase (COX) activity, profoundly influences tumor progression across various malignancies[132]. Consequently, COX inhibitors present promising candidates for synergistic immunotherapy against tumors. A Phase II trial investigates the efficacy of pembrolizumab (anti-PD-1), ipilimumab (anti-CTLA-4), and aspirin (COX inhibitor) in melanoma treatment (NCT03396952).

Also, targeting Chol metabolism shows promise in inhibiting tumor growth and restoring immune function in certain cancers. Chol-lowering drugs, particularly statins (HMGCR inhibitors), are of interest due to their favorable safety profiles and ability to inhibit the key enzyme in Chol synthesis. A prospective cohort trial (NCT05636592) is investigating the safety and efficacy of combining PD-1/PD-L1 antibodies with statins in advanced NSCLC patients.

In addition to their therapeutic potential, it is essential to acknowledge the potential toxic side effects associated with lipid metabolism drugs. While these agents hold promise in enhancing antitumor efficacy, their use may also lead to adverse effects, particularly concerning hepatotoxicity and metabolic dysregulation. Consequently, combinations with immunotherapies remain predominantly in preclinical research stages. For example, inhibitors like orlistat face pharmacological limitations and induce weight loss, precluding their development as systemic drugs[133]. Similarly, the clinical use of ET is restricted, with a previous trial for congestive heart failure terminated due to elevated liver transaminase levels[134]. In a melanoma mouse model with low microphthalmia-associated transcription factor, treatment with the SCD1 inhibitor A939572 unexpectedly induced invasion and lung metastasis[135]. Moreover, tissue-specific enrichment in the liver and adipose tissue may limit the potential applications of ACLY or SCD1 inhibitors in cancer therapy[136–138]. More notably, the response of various immune cells to alterations in lipid metabolism is not uniform.

In conclusion, there is growing evidence that regulating lipid metabolism, encompassing lipid uptake (Table 1)[91,128,139–142], synthesis (Table 1)[41,129,143–150], lipolysis (Table 1)[151–153], and FAO (Table 1)[114,154,155] within the immune compartment holds significant potential for the development of novel therapies that synergize with current immunotherapies.

However, the translation of these compounds into clinical practice remains challenging due to adverse effects, underscoring the importance of cautious consideration regarding their off-target effects and unexpected outcomes. Hence, careful consideration of the balance between therapeutic benefits and potential toxicities is crucial in the development and clinical application of lipid metabolism-targeting drugs for cancer therapy.

4. Nano-based drug delivery systems for lipid metabolism intervention in TME

The convergence of cancer immunotherapy, nanotechnology, and drug delivery offers avenues for combining immunotherapeutic strategies with lipid metabolic interventions. NDDSs provide controlled and targeted delivery of drugs with immunomodulatory or lipid metabolic remodeling properties, offering improved pharmacokinetics and reduced adverse effects[18,156,157]. Notably, NDDSs can be engineered to respond to physical stimuli (such as light) or biological stimuli (such as pH, ROS, temperature, enzymes, etc.) to achieve controlled and spatio-temporal drug release[158–160]. Additionally, combining lipid metabolism-altering NDDSs with minimally invasive therapeutic modalities such as photodynamic therapy (PDT), chemo-dynamic therapy (CDT), and sonodynamic therapy (SDT) enhances tumor immunogenicity and promotes an inflammatory TME, leading to synergistic immunotherapeutic effects[161–166].

Specifically, this part will focus on four aspects of modulating lipid metabolism programs in TME to highlight recent innovative strategies in the field of NDDSs development, which could synergize with tumor immunotherapy by precision target: (1) reprogramming lipid uptake (Table 2)[167–170]; (2) reprogramming lipolysis (Table 2)[171–174]; (3) reshaping FAO (Table 2)[175–183]; and (4) reshuffling of lipid composition on the cell membrane (Table 2)[184–190]. Overall, intervening lipid metabolism *via* NDDSs, could be an attractive strategy to simultaneously prevent cancer cell proliferation, and restoring immune cell killing function.

4.1. NDDSs for reprogramming lipid uptake in the TME

4.1.1. Reprogramming lipid uptake in tumor cells

Tumor cells often increase lipid uptake to fuel their rapid proliferation. Recent research highlights that obesity can downregulate PHD3, an enzyme that normally restricts the transport of LCFAs into mitochondria[191]. Consequently, cancer cells consume LCFAs as a primary energy source, diminishing the activation of $CD8^+$ T cells in the TME[59]. To counteract this immunosuppression in obesity, upregulating PHD3 has emerged as a promising strategy to reprogram lipid uptake. In this regard, an efficient polymeric gene carrier (HPD) has been developed. HPD, created by modifying polyethylenimine/ptoluenesulfonyl (PEI-Tos) complexes with hyaluronic acid (HA) for tumor cell targeting, effectively delivers a plasmid encoding PHD3 (pPHD3)[170]. Upon successful entry into tumor cells, HPD facilitates the release of pPHD3, thereby reducing lipid uptake and utilization. *In vivo* studies involving B16-F10 and MC38 tumor-bearing mice on the HFDs, HPD significantly increased the infiltration of $CD8^+$ T cells into the TME. Furthermore, HPD improved the responsiveness to ICB therapy. These findings underscore the potential of HPD as a promising approach to modulate lipid metabolism and enhance anti-tumor immune responses in obesity.

4.1.2. Reprogramming lipid uptake in immune cells

Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-resident immunosuppressive cells, such as M2-TAMs, MDSCs, and Tregs, which express high levels of CD36 for lipid uptake, promoting their differentiation and pro-tumorigenic functions[91,119,192–194]. To tackle the issue, Ma et al.[167] developed an ROS-responsive composite hydrogel platform (iFCuS-M/SSO@Gel) loaded with an inhibitor of ferroptosis suppressor protein 1 (iFSP1) and CD36 inhibitor (SSO) (Fig. 4A–C). This platform targets CD36 on TRICs' surfaces, suppressing lipid uptake and relieving their immunosuppressive phenotype, allowing $CD8^+$ T cell infiltration. Additionally, iFCuS-M/SSO@Gel enhances immunogenic cell death (ICD) *via* LPO, effectively suppressing tumor growth, recurrence, and metastasis in the 4T1 tumor model[195,196]. Similarly, many studies

Table 1 List of lipid-targeted therapies in combination with immunotherapy.

Target	Drug/ compound	Mechanism	Cancer type	Phase	Combined with immunotherapy	Ref.
CD36	JC 63.1	Anti-CD36 Ab	Melanoma	Preclinical	Anti-PD-1 Ab	91
	FA6-152	Anti-CD36 Ab	Acute myeloid leukemia	Preclinical	–	139
	SSO	CD36 inhibitor	HCC	Preclinical	Anti-PD-1 Ab	128
	ABT-510	Peptide mimetics of TSP-1	Solid tumors	Phase 1	Bevacizumab	NCT00586092
FABPs	MF6	FABP5 and FABP7 inhibitor	Melanoma	Preclinical	–	140
	BMS-309403	FABP4 inhibitor	Pancreatic cancer	Preclinical	–	141
FATPs	Lipofermata	FATP2 inhibitor	Lymphoma, Lewis lung carcinoma, colon carcinoma, Pancreatic cancer	Preclinical	Anti-CTLA-4 Ab Anti-CSF-1R Ab	142
FASN	ASC40	FASN inhibitor	HER2 positive Metastatic BC	Phase 2	Trastuzumab	NCT03179904
		FASN inhibitor	GBM	Phase 3	Bevacizumab	NCT05118776
	Orlistat	FASN inhibitor	HCC	Preclinical	Anti-PD-L1 Ab	129
SCD1	A939572	SCD1 inhibitor	Osteosarcoma	Preclinical	Anti-PD-1 Ab Adoptive cell therapy	143
	MF-438	SCD1 inhibitor	Esophageal squamous cell carcinoma	Preclinical	–	144
PPAR	Rosiglitazone	PPAR agonist	Solid tumor malignancies	Phase 2	Anti-PD-1 Ab	NCT04114136
	GW9662	PPAR inhibitor	Melanoma	Preclinical	Anti-PD-L1 Ab	145
	Pioglitazone	PPAR agonist	CRC	Preclinical	Anti-PD-1 Ab	146
	GW501516	PPAR agonist	Melanoma	Preclinical	Adoptive cell therapy	147
	Fenofibrate	PPAR agonist	Melanoma	Preclinical	Adoptive cell therapy	148
	Bezafibrate	PGC-1α/PPAR agonist	NSCLC	Preclinical	Nivolumab	149
COX	Aspirin	COX inhibitor	Head and neck cancer	Phase 1	Anti-PD-1 Ab	NCT03245489
		COX inhibitor	TNBC	Phase 2	Anti-PD-L1 Ab	NCT04188119
		COX inhibitor	Melanoma	Phase 2	Anti-CTLA-4 Ab Anti-PD-1 Ab	NCT03396952
		COX inhibitor	Ovarian neoplasms	Phase 2	Anti-PD-L1 Ab Atezolizumab Bevacizumab	NCT02659384
HMGCR	Statin	HMGCR inhibitor	Lung cancer	Prospective cohort	Anti-PD-1/PD-L1 Ab	NCT05636592
SREBP	Fatostatin	SREBP inhibitor	Melanoma	Preclinical	Anti-PD-1 Ab	150
ACLY	ETC-1002	ACLY inhibitor	Pancreatic cancer Melanoma	Preclinical	Anti-PD-L1 Ab	41
DGAT	A922500	DGAT inhibitor	Melanoma	Preclinical	–	151
	AZD3988	DGAT inhibitor	BC	Preclinical	–	152
HSL	HSL-IN-1	HSL inhibitor	HCC	Preclinical	–	153
CPT1	ET	CPT1 inhibitor	GBM	Preclinical	Anti-CD47 Ab	114
	Perhexiline	CPT1 inhibitor	HCC	Preclinical	–	154
	Ranolazine	FAO inhibitor	Melanoma	Preclinical	Anti-PD-L1 Ab	155

–, not applicable. Ab, antibody; HCC, hepatocellular carcinoma; FABPs, fatty acid binding proteins; FATP, fatty acid transport proteins; FASN, FA synthase; BC, breast cancer; GBM, glioblastoma multiforme; SCD, stearoyl-CoA desaturase; PPAR, peroxisome proliferator-activated receptor; CRC, colorectal cancer; PGC, peroxisome proliferator-activated receptor gamma coactivator; NSCLC, non-small cell lung cancer; COX, cyclo-oxygenase; TNBC, triple negative breast cancer; HMGCR, HMG-CoA reductase; SREBP, sterol regulatory element-binding proteins; ACLY, ATP-citrate lyase; DGAT, diglyceride acyltransferases; HSL, hormone-sensitive lipase; CPT1, carnitine palmitoyltransferase 1; FAO, fatty acid oxidation.

have shown that the cytotoxic activity of $CD8^+$ T cells is impaired by energy deprivation[197]. For this reason, an amphiphilic nanoparticle encapsulating PPARα activator (fenofibrate) surface-modified anti-CD3e f (ab')2 fragment was designed to target T cells[169]. The increased uptake of fluorescent labeled lipids by aCD3/F/AN-treated T cells may be due to upregulation of CD36 by fenofibrate. Consequently, both *in vitro* and *in vivo* experiments have demonstrated that aCD3/F/AN has an efficient cytotoxic effect against B16-F10 melanoma cells by reprogramming the lipid metabolism in T-cells.

Conversely, tumor-antagonizing immune cells like DCs, NK cells, and $CD8^+$ T cells can also be functionally impaired by excessive lipid uptake. To address this issue, Xu et al.[168] designed a multi-level lipid reprogramming micelle for TIDCs activation (TS-PP@FU). This micelle, constructed with ACC inhibitor (TOFA), XBP1 mRNA splicing inhibitor (STF-083010), and amphiphilic block copolymer (PCL-PEI), targets the lipid

Table 2 List of Nano-based drug delivery systems for lipid metabolism intervention in TME.

Strategy for lipid metabolism	NDDS	Type	Cargo	Target and function	Targeted cell type	Cancer type	Ref.
Lipid uptake	iF-CuS-M/SSO@Gel	Composite hydrogel; hollow mesoporous CuS NPs	SSO, FSP1 inhibitor	CD36, FSP1 Lipid uptake	Tumor cell and immunosuppressive cells	TNBC: 4T1 cells	167
	TS-PP@FU	Self-assembled NPs	TOFA, STF, FU	ACC, XBP1, MSR1 Lipid uptake; Endogenous lipid generation	Tumor-associated DCs	TNBC: 4T1 cells	168
	aCD3/F/ANs	Ab conjugation of NPs	Fenofibrate	PPARα Lipid uptake; FAO	$CD8^+$ T cells	Melanoma: B16-F10 cells	169
	HA/PEI-Tos/pDNA	Polymeric gene delivery NPs	PHD3 plasmid	PHD3 Lipid uptake and utilization	Tumor cell and $CD8^+$ T cells	Melanoma: B16-F10 cells Colorectal tumor: MC38 cells	170
Lipolysis	NPs(siMGLL/siCB-2)	Polymeric gene delivery NPs	MGLL siRNA and CB-2 siRNA	MGLL, CB-2 Lipolysis	Tumor cell and M2-TAMs	PDAC: LTPA cells	171
	DOX + RA@adipocytes	Biomimetic delivery system	RA and DOX prodrug	Adipocytes Lipolysis	Tumor cell	Melanoma: B16-F10 cells	172
	pTP-Ce6-Apo	Biomimetic delivery system	PA-triptolide derivative and Ce6	Adipocytes Lipolysis	Tumor cell	Melanoma: A375 cells	173
	Liposome-Ma	Liposome	Matairesinol	PNLIP, DGAT2 TG hydrolysis and resynthesis	Tumor cell	CRC: HCT116 cells	174
FAO	PCL/PTX@DSPE/ET	Micellar system	PTX and ET	CPT1A FAO	Tumor cell and M2-TAMs	TNBC: 4T1 cells	175
	Ato/siP@SLNP	Self-assembled lipopeptide nanoplexes	Atorvastatin	GPAT1, AMPK Lipolysis and FAO	Tumor cell	Melanoma: B16-F10 cells CRC: CT26 cells	176
	α-T-K	Nanoemulsion	KIRA6, α-tocopherol	ER stress, oxidative stress FAO	M2-TAMs	TNBC: 4T1 cells Lung cancer: LLC cells	177
	MSNPs	Liposomal	R848, ET	TLR7/8, CPT1A FAO	M2-TAMs	TNBC: 4T1 cells	178
	TA-Met@MS	Hollow gold nanospheres into microspheres	Tumor antigen, metformin	AMPK FAO	Tmems	TNBC: 4T1 cells Melanoma: B16-F10 cells	179
	CTS/p (I:C)-MMA	Biomimetic delivery system	Viral RNA analog and Cryptotanshinone	CPT1 FAO	Tumor-infiltrating DCs and M2-TAMs	TNBC: 4T1 cells Ovarian cancer: ID8 cells	180
	Ato/CQ@L	Liposome	Atorvastatin and chloroquine	AMPK, CPT1A, LC3B FAO	Tumor cell	TNBC: 4T1 cells	181
	Pt (IV)/CQ/PFH NPs-^{D}PPA-1	Liposome	Pt (IV), Perfluorohexane, Chloroquine	FAO	Tumor cell and M2-TAMs	TNBC: 4T1 cells	182
	VFETX	Self-assembly nanodrug	Vitamin B1, ferrous ions, and ET	CPT1 FAO	Tumor cell	CRC: CT26 cells	183
Reshuffling of lipid composition	Micelles/RSL3	Micelles	AA; RSL3	GPX4, LPO	Tumor cell	Ovarian adenocarcinoma: NCI/ADR-Res or NAR cells	184

on the cell membrane	IO-LAHP NPs	Iron oxide NPs	Linoleic acid hydroperoxide	Hydroxyl radical LPO	Tumor cell	Malignant gliomas: U87MG cells 185
	FeCo/Fe−Co DAzyme/PL	Single-atom nanozymes	LOX and PLA2	PLA2, LOX, ACSL4, GPX4 LPO	Tumor cell	TNBC: 4T1 cells 186
	HLCaP NRs	$CaCO_3$-assisted double emulsion	Lipoxidase and hemin	LOX LPO	Tumor cell	TNBC: 4T1 cells 187 HCC: H22 cells
	EALP	Nanovesicle	Photosensitizer pheophorbide A and AVA	ACAT-1 Enhanced level of Chol on membrane	Tumor cell	Melanoma: B16F10 cells 188
	T-Tre/BCN-Lipo-Ava cells	Biomimetic delivery system	AVA	ACAT-1 Enhanced level of Chol on membrane	$CD8^+$ T cells	Melanoma: B16-F10 cells 189 GBM: LN229 cells
	Gel@NPs	Hydrogel delivery system	Rosuvastatin	HMGCR Chol metabolism	Tumor cell	Melanoma:B16-OVA cells 190

NPs, nanoparticles; TNBC, triple negative breast cancer; ACC, Ac-CoA carboxylases; XBP1, X-box binding protein 1; MSR1, macrophage scavenger receptor 1; DCs, dendritic cells; Ab, antibody; PPARα, peroxisome proliferator-activated receptor alpha; FAO, fatty acid oxidation; PHD3, prolyl hydroxylase-3; MGLL, monoglyceride lipase; CB-2, endocannabinoid receptor-2; TAMs, tumor-associated macrophages; PDAC, pancreatic ductal adenocarcinoma; RA, rumenic acid; DOX, doxorubicin; PA, palmitate; DGAT, diglyceride acyltransferases; CRC, colorectal cancer; PTX, paclitaxel; ET, etomoxir; CPT1, carnitine palmitoyltransferase 1; GPAT1, glycerol-3-phosphate acyltransferase-1; AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; AA, arachidonic acid; LPO, lipid peroxidation; LOX, lipoxygenase; AVA, avasimibe; Chol, cholesterol; GBM, glioblastoma multiforme; HMGCR, HMG-CoA reductase.

transport receptor MSR1 on TIDCs (Fig. 4D−E). TS-PP@FU restricts nuclear lipogenic gene transcription, cytoplasmic DNL, and extracellular lipid uptake (Fig. 4F−H). *In vivo* studies demonstrated that TS-PP@FU, in combination with anti-PD-1 therapy, effectively reduces TIDCs, recruits cytotoxic T cells, and inhibits 4T1 tumor survival through comprehensive lipid metabolic reprogramming.

4.2. *NDDSs for reprogramming lipolysis in the TME*

Tumor cells exhibit a propensity to store lipids in LDs, which can be hydrolyzed into FFAs to serve as a source of ATP and essential components of biological membranes[198,199]. This process is mediated by three rate-limiting enzymes: triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGLL).

Recent research has highlighted the high expression of MGLL in tumor cells. However, inhibiting MGLL can lead to the secretion of 2-arachidonoylglycerol (2-AG) into the TME, promoting the transition of M2-TAMs *via* stimulation of the endocannabinoid receptor-2 (CB-2) (Fig. 5B and C)[200,201]. To address this challenge, Cao et al.[171] developed reduction-responsive polymer nanoparticles (NPs) co-encapsulating MGLL siRNA (siMGLL) and CB-2 siRNA (siCB-2), coated with DSPE-PEG3000 (Fig. 5A). These NPs (siMGLL/siCB-2) achieved simultaneous suppression of FFAs generation by siMGLL in PDAC cells and repolarization of TAMs into an M1-like phenotype by siCB-2. Treatment with NPs (siMGLL/siCB-2) significantly inhibited tumor progression and prolonged survival in PDAC models (Fig. 5D−E).

Additionally, CAAs are actively involved in lipolysis, induced by tumor cells to release FFAs as a primary energy source[118,119]. To exploit this phenomenon, Wen and colleagues[172] engineered adipocytes (referred to as pDox + RA@adipocytes) to act as a drug delivery depot at the tumor site (Fig. 5F). These adipocytes contain anti-cancer FA (rumenic acid, RA) and a ROS-responsive doxorubicin prodrug (pDox) within their LDs, which are released through lipolysis at the tumor site (Fig. 5G). Treatment with pDox + RA@adipocytes resulted in the downregulation of PD-L1 expression, activation of $CD4^+$ and $CD8^+$ T cell-mediated immune responses, and enhanced tumor cell apoptosis in a B16-F10 tumor model. Similarly, mature adipocytes loaded with a glutathione (GSH)-responsive palmitic acid-conjugated triptolide derivative (pTP) and the photosensitizer Ce6 (referred to as pTP-Ce6-Apo) were developed to target melanoma metastasis[173]. Upon lipolysis induced by intracellular GSH and laser irradiation, pTP-Ce6-Apo releases pTP and Ce6, leading to the abundant generation of cytotoxic ROS and ER stress. *In vivo* experiments demonstrated that pTP-Ce6-Apo effectively inhibited tumor growth and metastasis of melanoma with high biosafety following para-tumor injection.

4.3. *NDDSs for reshaping FAO in TME*

Recent interest has focused on interventions targeting cellular energy metabolism, eliciting potent anti-cancer immune responses in the TME. Notably, FFAs and mitochondrial FAO are crucial energy sources for both immune and tumor cells. Here, we discuss nanomedicine strategies aimed at reprogramming FAO-linked cancer therapies and immunotherapies.

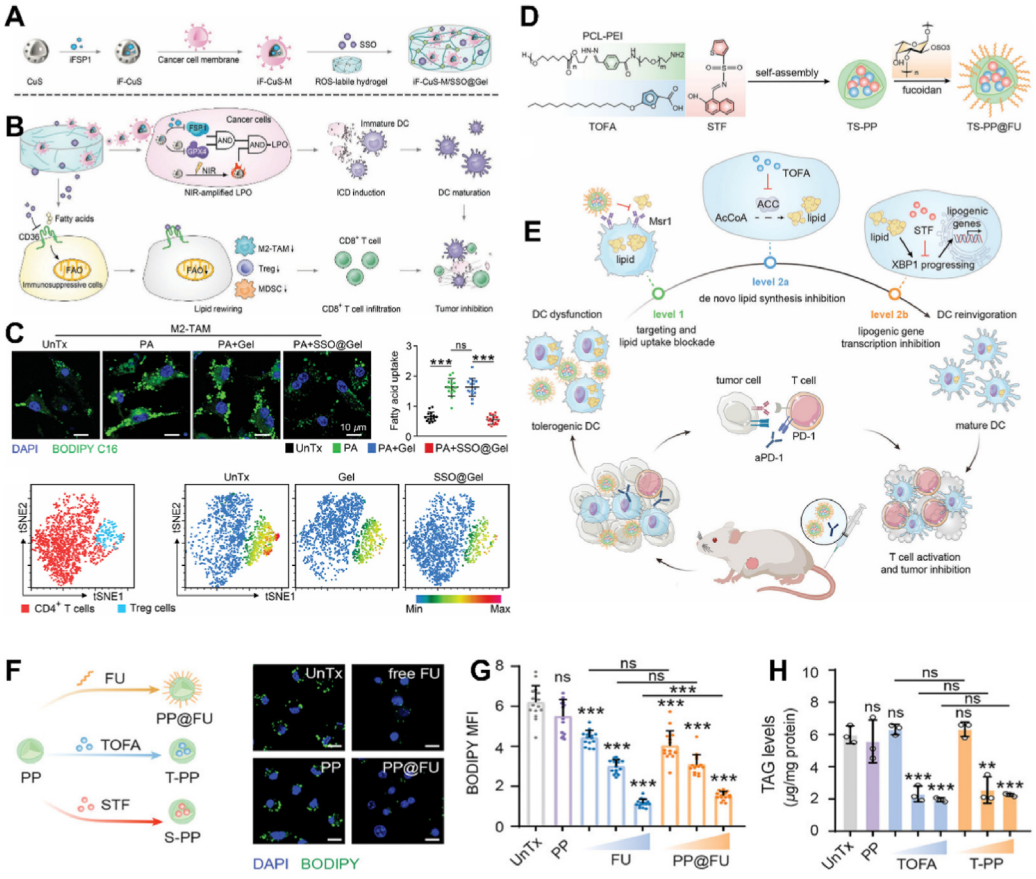

Figure 4 NDDSs for rewriting lipid uptake in TME. (A) Synthesis and (B) mechanism of iFCuS-M/SSO@Gel for enhancing antitumor immunity by simultaneously modulating lipid uptake of immunosuppressive cells and inducing ferroptosis in 4T1 cells. (C) Fluorescent imaging and quantification of FFAs uptake by M2-TAMs from SSO@Gel (scale bar = 10 μm). Additionally, the levels of tumor-infiltrating Treg cells in the t-SNE map treated by SSO@Gel were examined. Reprinted with the permission from Ref. 167. Copyright © 2023 Wiley. (D) Preparation and (E)mechanism of TS-PP@FU for boosting antitumor immunity by targeting TADC and multilevel lipid metabolic reprogramming. (F) Fluorescent imaging, (G) quantification of BODIPY-stained lipids (n = 15, scale bar = 20 μm) and (H) the TAG levels in PA-stimulated DCs after indicated treatment (n = 3). Data are presented as mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$, ns, not significant. Reprinted with the permission from Ref. 168. Copyright © 2023 Wiley.

4.3.1. *Reshaping FAO in cancer cells*

Since FAO is significantly diminished in cancer cells, potentiating FAO to avoid oxidative damage from elevated ROS levels is a novel strategy for sustained tumor cell killing. Therefore, Gao and collaborators[176] have developed a pH/redox dual-responsive NDDS (Ato/siP@SLNP) to co-encapsulate the FAO activator (atorvastatin, Ato) and a PD-L1 small interfering RNA (PD-L1 siRNA) in the lipopeptide nanoplexes (Fig. 6A). Ato can accelerate the AMP-activated protein kinase (AMPK)-CPT1a axis and inhibit TGA synthesis by the glycerol-3-phosphate acyltransferase-1 (Gpat1) expression to boost the highly restrained FAO for ROS production (Fig. 6B). *In vivo* experiments showed that the self-amplified ROS production mediated by A to/siP@SLNP not only induced ICD to elicit strong antitumor immune responses but also enhanced the anti-tumor effectiveness of PD-L1 siRNA in melanoma and CRC models (Fig. 6C).

In another independent study, it was found that lymph node metastatic tumor cells adapted metabolically to FAO in lipid-rich lymph nodes[175]. Based on this concept, a matrix metalloproteinase-2-responsive micellar system (PCL/PTX@DSPE/ET) has been developed for precise drug delivery to the tumor-draining lymph nodes (TDLNs). This NDDS can sequentially deliver paclitaxel (PTX) and ET to inhibit the primary tumors and lymphatic metastasis. On the one hand, PCL-PEG/PTX could kill tumor cells *in situ* and block M2-TAMs polarization, alleviating the immunosuppress TME. On the other hand, the small satellite micelle encapsulating ET (DSPE-PEG/ET, ~10 nm) could accumulate in lymph nodes and block the FAO of tumor cells, thereby inhibiting lymphatic metastasis in TNBC model.

4.3.2. *Reshaping FAO in immune cells*

To drive TAMs from a pro-tumor (M2) to an anti-tumor (M1) phenotype by modulating their energy metabolism, a reductive nano-emulsion (α-T-K) was developed by Jiang et al.[177] This nano-emulsion includes KIRA6, an inhibitor of ER stress, and α-tocopherol, an oxidative stress inhibitor. α-T-K targets the IRE1-XBP1 pathway associated with ER stress, boosting glycolysis and decreasing FAO in M2-TAMs. Combined with α-tocopherol's inhibition of ROS, α-T-K effectively shifts M2-TAMs towards an M1 phenotype under hypoxia, thereby slowing tumor proliferation and enhancing the efficacy of anti-PD-1 therapy in breast and lung cancer models. Similarly, a metabolic supramolecular nanoparticle (MSNPs) was designed to reprogram lipid metabolism in TAMs, thereby alleviating the TME[178]. MSNPs deliver the Toll-like

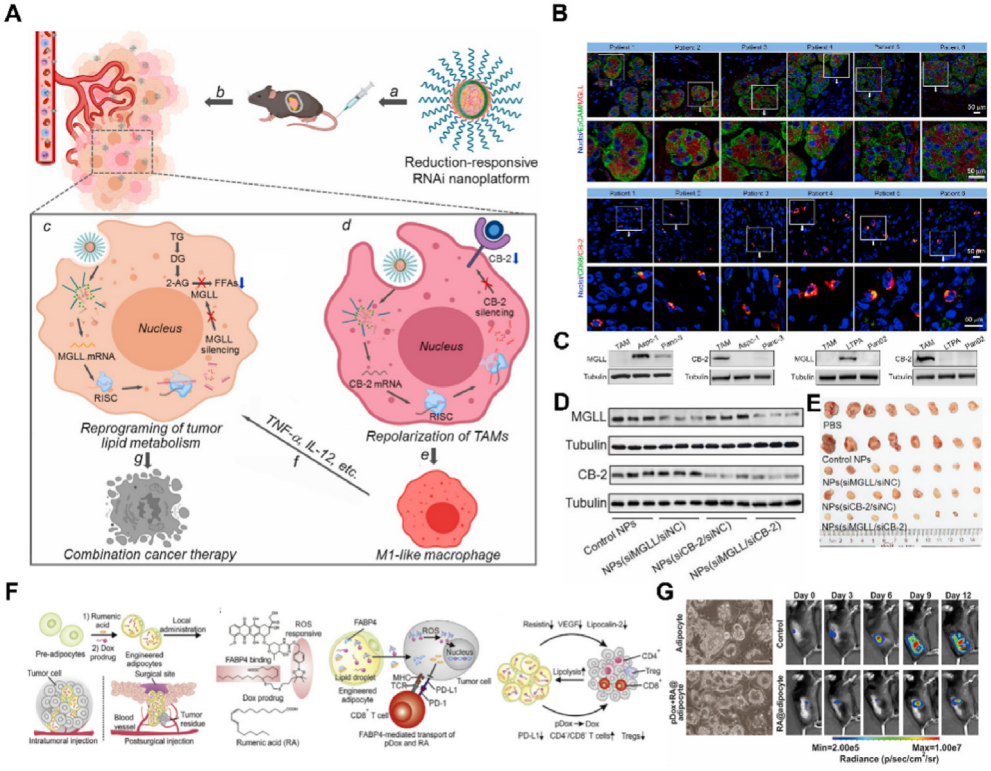

Figure 5 NDDSs for reprogramming lipolysis in the TME. (A) Illustration of the NPs (siMGLL/siCB-2) and its functions for simultaneous suppression of FFAs generation and repolarization of TAMs in PDAC models. (B) Immunofluorescence of MGLL and CB-2 in the tumor tissues of PDAC patients (scale bar = 50 μm). (C) The protein expression of MGLL and CB-2 in tumor cell lines and tumor tissue. (D) The expression of MGLL and CB-2 in tumor tissues treated with various therapies. (E) Photographs of tumors treated with NPs (siMGLL/siCB-2) in the PDAC model (n = 8). Reprinted with the permission from Ref. 171. Copyright © 2022 Elsevier. (F) Preparation and proposed mechanism of engineered adipocytes (pDox + RA@adipocytes) to potent ICB-based tumor immunotherapy. (G) Representative figures and tumor bioluminescence of pDox + RA@adipocytes (scale bar = 200 μm). Reprinted with the permission from Ref. 172. Copyright © 2019 Elsevier.

receptor 7/8 agonist R487 and the FAO inhibitor ET, stimulating glycolysis and redirecting the TCA cycle to polarize TAMs towards M1 phenotype. *In vivo* studies demonstrated enhanced M1/M2 repolarization by MSNPs, impeding tumor progression.

The critical indicator of a successful tumor vaccine is priming the immune system to generate more memory $CD8^+$ T cells (Tmems), which are essential weapons for long-term protective immunity[202,203]. Evidence has emerged that the formation of Tmems requires a switch in the metabolic pattern of effector $CD8^+$ T cells (Teffs) from glycolysis to FAO[204–206]. Based on this concept, Luo et al.[179] developed a nanovaccine vector (TA-Met@MS) for synergistically enhancing PTT-induced ICD and immune memory. The TA-Met@MS was the poly (lactic-*co*-glycolic acid) (PLGA) microspheres, which constructed by tumor antigen (TA), metformin (Met), and hollow gold nano-spheres (HAuNS). Importantly, altering the metabolic behavior of Teffs from glycolysis to FAO by Met improved Teffs survival, while facilitating the differentiation of Tmems. Remarkably, TA-Met@MS exhibits potent preventive efficacy in various tumor models and significantly inhibits lymph node metastasis *in vivo*.

4.4. *NDDSs for reshuffling of lipid composition on the cell membrane in TME*

The degree of FA desaturation executes important physiological roles in the components of cell membranes and fluidity. The most abundant type of membrane lipid is the PLs[207]. In principle, SFA-PLs increase membrane rigidity, while higher unsaturated PLs make membranes more flexible. Increasing the content of PUFA-PLs in the cell membrane can enhance cell fluidity. However, it also heightens the vulnerability to ferroptosis, a process of cell death caused by iron-LPO. Hence, cancer cells display elevated SFA-PLs, which not only increases membrane rigidity but also protects against peroxidation induced by ROS. The main PUFA is the ω-6 PUFA LA and AA. In this perspective, reshuffling of lipid composition by NDDS on the tumor membrane could promote the ferroptosis.

The presence of externally supplied AA would enhance intracellular levels of the inducing precursor of ferroptosis. Gao and co-workers[184] synthesized the polymer micelles which are made of AA-conjugated amphiphilic copolymer and loaded the potent ferroptosis inducer, RSL3 to trigger ferroptosis for persistent cancer cells (PCCs) removal both *in vitro* and *in vivo*. Equally notable is that $CD8^+$ T cells derived IFNγ and the AA from the TME can make tumor cells more sensitive to ferroptosis by long chain acyl-CoA synthetase 4 (ACSL4)[208,209]. Therefore, Liu et al.[186] designed a cascade immunogenic nanoplatform (FeCo/Fe-Co DAzyme/PL) to trigger ferroptosis in tumor cells (Fig. 7A). The FeCo/Fe-Co DAzyme/PL was co-loaded with lipoxygenase (LOX) and phospholipase A2 (PLA2). The nanoplatform obtained has the ability to induce initial immunogenic tumor ferroptosis through its multi-enzyme mimetic activities. It also up-regulates AA levels by PLA2 to synergize with the IFNγ produced by $CD8^+$ T cells,

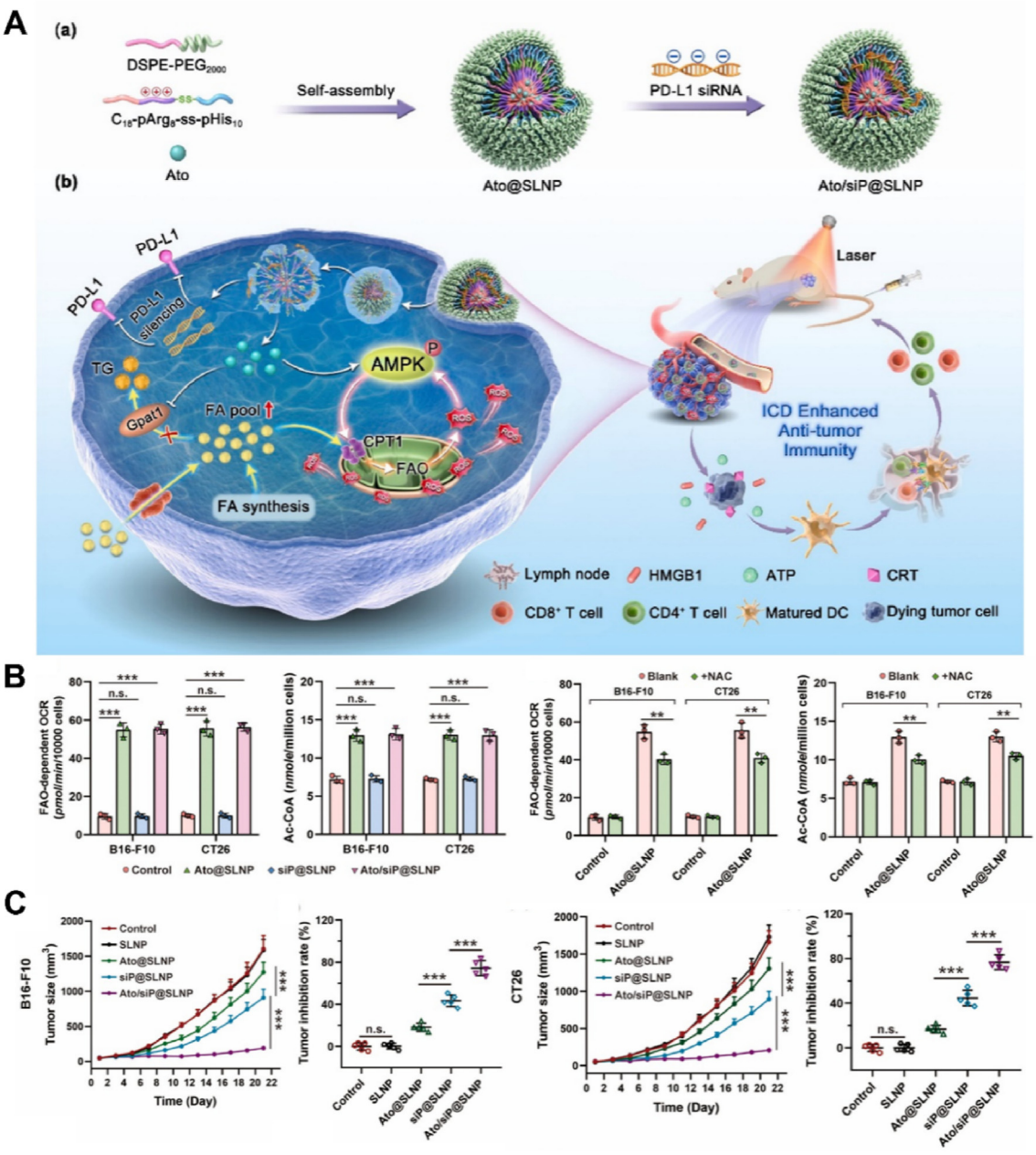

Figure 6 NDDSs for reshaping FAO in the TME. (A) Schematic illustration of the preparation and mechanism of Ato/siP@SLNP for promoting FAO to produce ROS and improving the anti-tumor effectiveness of PD-L1 siRNA. (B) The FAO-dependent OCR and intracellular levels of Ac-CoA in tumor cells treated with Ato/siP@SLNP was analyzed ($n = 3$). (C) Tumor volume and the inhibition rate ($n = 5$). Data are presented as mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$, ns, not significant. Reprinted with the permission from Ref. 176. Copyright © 2022 Elsevier.

generating ROS, and depleting GSH and GPX4 to induce an irreversible cascade of immunogenic ferroptosis in the 4T1 tumor-bearing mouse model (Fig. 7B and C). In a separate investigation, Yu et al.[210] delineated the utilization of a high-intensity focused ultrasound (HIFU)-driven nanomotor (NP-G/P) to induce LPO and ferroptosis in TNBC. NP-G/P, comprising PLGA NPs encapsulating perfluorooctyl bromide and the ferroptosis-inducing agent gambogic acid, was engineered to be responsive to HIFU irradiation. This approach facilitated the induction of ferroptosis and subsequent activation of antitumor immunity in both primary and metastatic TNBC models. Similarly, the combination of dihydroartemisinin (DHA)-loaded magnetic NPs (Fe_3O_4-PGA-DHA) with doxorubicin (DOX)-loaded magnetic NPs (Fe_3O_4-PASP-DOX) was explored for TNBC chemotherapy, leveraging the mechanism of LPO[211].

In additional, lipids, especially Chol also contribute to membrane properties by regulating membrane fluidity and permeability[12]. Chol is generated from isoprenoid precursors produced by the mevalonate pathway[212,213]. Chol modulates membrane fluidity and permeability and enhances activated $CD8^+$ T cell interaction with MHC, promoting T cell receptor (TCR) clustering and immune responses[214]. Given the vital role of Chol in both tumor cells and $CD8^+$ T cells, NDDSs that re-programme Chol synthesis have recently attracted a lot of interest in the immunotherapy of cancer. Liu et al.[188] developed the tumor-penetrable nanovesicle (named as EALP) to block

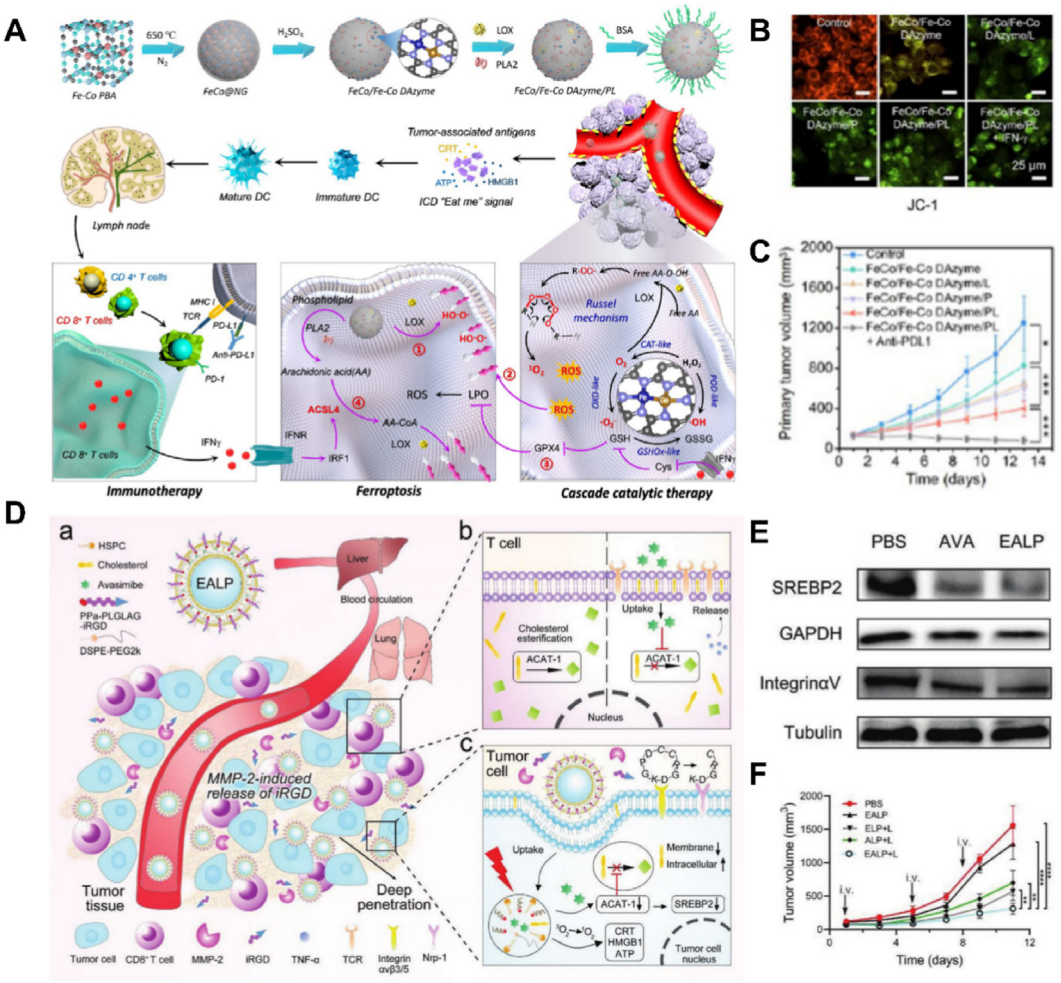

Figure 7 NDDSs for reshuffling of lipid composition on the cell membrane in the TME. (A) Illustration of the FeCo/Fe-Co DAzyme/PL and its mechanism to induce cascade immunogenic ferroptosis. (B) Detection of mitochondrial membrane potential after different treatments (scale bar = 25 μm); (C) Changes in tumor volume after different treatments. Reprinted with the permission from Ref. 186. Copyright © 2023 American Chemical Society. (D) The preparation and mechanism of EALP (E) The expression of SREBP2 and IntegrinaV in tumor tissue. (F) Tumor growth ($n = 5$). Data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Reprinted with the permission from Ref. 188. Copyright © 2023 Wiley.

the Chol esterification for enhancing PDT-mediated cancer immunotherapy (Fig. 7D). EALP releases avasimibe (AVA) to enhance the level of Chol on membrane and improving TCR signaling (Fig. 7E). EALP shows superior tumor growth induction in the B16-F10 mouse model (Fig. 7F). Similarly, AVA-liposomal clicked onto the T cell surface (T-Tre/BCN-Lipo cells) was designed by Hao and her colleges[189]. The local release of AVA could increase the concentration of Chol in the T-cell membrane, leading to a fast TCR clustering and prolonged T-cell activation. In the models of melanoma and GBM, T-Tre/BCN-Lipo cells resulted in superior antitumor efficacy without significant systemic side effects. Encouragingly, NDDSs-induced lipid composition rearrangement on cell membranes hold promise for enhancing antitumor efficacy and ICB therapy.

5. Conclusions and outlooks

The alteration of lipid metabolism has emerged as a pivotal target for cancer therapy, particularly within the realm of immunotherapy. Cancer cells undergo substantial reprogramming of lipid metabolism, including heightened lipid uptake, synthesis, lipolysis, FAO, and storage, all geared toward promoting their survival and proliferation. Furthermore, the TME undergoes remodeling that impacts lipid metabolism and the functional phenotypes of TRICs. In light of recent discoveries concerning tumor immune evasion and resistance to therapy, the review focuses on elucidating the role of both endogenous and exogenous lipids in modulating tumor immunity by influencing the behavior of cancer and immune cells.

Despite significant progress, several major limitations must be addressed before clinical trials. These include the lack of targeted drugs for lipid metabolism modulation, with only a few inhibitors currently in clinical trials. The dual role of lipids in the TME necessitates careful consideration when targeting the lipid metabolism of TRICs. Cancer cells' adaptation to single lipid interventions by exploiting compensatory pathways highlights the need for targeting multiple cellular metabolisms simultaneously. Moreover, the impact of environmental factors such as obesity on tumor immune responses warrants further research.

In recent decades, NDDSs have rapidly gained prominence in cancer research, particularly for intervening in tumor lipid metabolism[215,216]. Key aspects include blocking lipid uptake by NDDSs, which can inhibit tumor cells and immunosuppressive

TRICs, reduce lipotoxicity in immune killer cells, and promote immune surveillance in the TME. Additionally, suppressing lipolysis of LDs to inhibit nutrient supply and biological membrane formation in tumor cells, while utilizing the lipolysis property of CAAs for effective drug delivery. Rational design of NDDSs to release drugs for precise reprogramming of FAO is also emphasized. Furthermore, inducing recombination of lipid composition and desaturation on the cell membrane to increase ferroptosis and immunogenicity, thereby enhancing antitumor immunity.

However, the development of NDDSs aimed at regulating lipid metabolism requires a focused strategy, emphasizing the precise identification of tumor or immune cell-specific surface markers. By incorporating endogenous or exogenous stimuli response strategies into their design, these systems can enhance drug bioavailability while minimizing adverse effects. Overcoming barriers such as those posed by blood circulation and the TME is crucial for ensuring the effective accumulation and penetration of NDDSs within tumors.

The investigation into lipid involvement in cancer therapy began in the 1980s, focusing on lipid signaling and metabolism in cancer cells. In the 1990s, liposomes, lipid-based nanoparticles, were explored as drug delivery systems to improve chemotherapy's efficacy while minimizing side effects. By the 2000s, lipid-based immunotherapies emerged, leveraging lipid antigens for activating immune responses against tumors. These advances led to the development of lipid vaccines and immunomodulatory agents. Throughout the 2010s, lipidomics provided deeper insights into cancer cell lipid metabolism, identifying new lipid targets for therapy. This period saw the emergence of lipid-targeting drugs and lipid-based immunotherapies, with lipid nanoparticles used for targeted drug delivery and lipid-modifying enzymes investigated as anticancer agents. Moreover, lipid-based immunotherapies, including vaccines and antibodies targeting lipids, underwent preclinical and clinical evaluation for their efficacy in cancer treatment and immunotherapy.

Overall, lipid metabolism holds great promise in immuno-oncology, presenting opportunities for tailored therapeutic interventions. NDDSs play a pivotal role in this domain by providing a platform for the delivery of targeted therapies that can enhance patient care and prognosis in cancer therapy. Ongoing research and innovation in this field are essential for fully realizing the therapeutic benefits of targeting lipid metabolism in cancer treatment.

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Author contributions

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Conflicts of interest

The authors have no conflicts of interest to declare.

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