Reprogramming the immunosuppressive tumor microenvironment through nanomedicine: an immunometabolism perspective

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Summary

Increasing evidence indicates that immunotherapy is hindered by a hostile tumor microenvironment (TME) featured with deprivation of critical nutrients and pooling of immunosuppressive metabolites. Tumor cells and immunosuppressive cells outcompete immune effector cells for essential nutrients. Meanwhile, a wide range of tumor cell-derived toxic metabolites exerts negative impacts on anti-tumor immune response, diminishing the efficacy of immunotherapy. Nanomedicine with excellent targetability offers a novel approach to improving cancer immunotherapy via metabolically reprogramming the immunosuppressive TME. Herein, we review recent strategies of enhancing immunotherapeutic effects through rewiring tumor metabolism via nanomedicine. Attention is drawn on immunometabolic tactics for immune cells and stromal cells in the TME via nanomedicine. Additionally, we discuss future directions of developing metabolism-regulating nanomedicine for precise and efficacious cancer immunotherapy.

Keywords: Metabolic reprogramming; Immunometabolism; Anti-tumor immunity; Tumor immune microenvironment; Nanomedicine

Introduction

In recent decades, immunotherapy has achieved remarkable clinical breakthroughs and gained popularity in treating cancer.[1] However, the overall response to immunotherapy is usually impeded by an immune-resistant tumor microenvironment (TME). Specifically, tumor cells rewrite their metabolism and create a TME featured with critical nutrient deficiency and immunoinhibitory metabolite accumulation, inhibiting antigen presentation by dendritic cells (DCs) and deactivating the tumor-killing function of cytotoxic T lymphocytes (CTLs) and natural killer cells (NK cells). Moreover, immunosuppressive cells such as tumor associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and cancer-associated fibroblasts (CAFs) can readily adapt themselves to the nutritionally deprived TME due to their metabolic flexibility, and after adaptation, they often become accomplices in tumor immune evasion. In this context, metabolic reprogramming of the TME could be a promising strategy to enhance anti-tumor immunotherapeutic effects,[2] and fully elucidating the intertwined metabolic networks among various cells in the TME is essential for performing targeted immunometabolic therapy.

To metabolically reprogram the immune-resistant TME, the use of nanomedicine has emerged as a promising approach. On the one hand, nanomaterials improve targetability, pharmacokinetics and bioavailability of delivered small molecular metabolic regulators, thereby enhancing the efficacy of immunometabolic therapy while reducing adverse effects.[3] On the other hand, nanomaterials in synergy with other cancer treatment modalities like radiotherapy, which often induces tumor immunogenic cell death (ICD) to facilitate release of disease-associated molecular patterns (DAMPs) and activate immune cells, bolstering immunotherapy outcomes.[4,5] Encouragingly, nanomedicine-mediated tumor cell-targeting immunotherapies have been progressively explored, while metabolic manipulation of immune cells and stromal cells via nanomedicine to rebuild an immunocompetent TME remains to be discovered. Leveraging engineered nanomaterials to deliver metabolic modulators to non-tumor cells in the TME has the potential to offer more precise and potent therapeutic methods.

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Herein, we initially elaborate the impact of metabolic reprogramming of tumor cells and stromal cells on immunocompetent cells from the aspects of nutrient deprivation and suppressive metabolite accumulation. Next, we survey the current landscape of therapies by harnessing nanomedicine to manipulate tumor metabolism to overcome the barriers in the TME. In addition, the potential of nanomedicine to revitalize the immunosuppressive TME by modulating metabolism of immune cells as well as stromal cells is elaborated. Finally, forward-looking strategies for enhancing nanomedicine-assisted immunometabolic therapies are offered. Overall, we discuss nanomedicine-assisted metabolic reprogramming strategies to regulate an immunosuppressive TME, paving a way for efficacious cancer immunotherapy.

Metabolic profiles in the immunosuppressive TME

Tumor cells are capable of rewriting their metabolic profiles to consume more nutrients to promote macromolecule biosynthesis and maintain redox homeostasis, thus facilitating rapid cell proliferation and tumor metastasis. Interestingly, tumor cells prefer aerobic glycolysis, an inefficient way of generating energy, over oxidative phosphorylation (OXPHOS) to generate intermediate metabolites for biosynthesis, known as the "Warburg effect". Besides, tumor cells adaptively consume certain non-essential amino acids including glutamine and arginine that are also indispensable for activation of the tumor-lysis function of immune effector cells. For example, metabolically active tumor cells overexpress nitric oxide synthase 2 (NOS2) to consume excessive arginine, which negatively impacts the survival of T cells.[6] Lipids not only provide tumor cells with building blocks for cell membranes, but also provide ATP during energy stress. It is recently discovered that oxysterols and prostaglandin E2 (PGE2), the lipid derivatives, display immunosuppressive properties and promote tumor immune evasion.[7,8] In addition, abundant adenosine leads to unsatisfactory immunotherapeutic effects.[9,10]

Altered tumor metabolism impairs immune cells in various ways (Fig. 1). Notably, increasing attention has been drawn to stromal cell metabolism, especially CAFs, the most abundant and heterogeneous stromal cells within the TME. The metabolism of CAFs favors tumor immune evasion via supplying metabolites to tumor cells and deteriorating nutrient deprivation. For glucose metabolism, tumor compressive and oxidative stress upregulate glycolysis and promote lactate production in CAFs, and CAF-derived lactate can be recycled by tumor cells to generate energy and nutrients.[11–13] For amino acid metabolism, CAFs can rewrite their metabolic product profiles and supply glutamine, arginine and aspartate to tumor cells.[14–16] Additionally, CAFs can consume SAM to downregulate histone methylation in ovarian cancer cells, promoting tumor metastasis.[17] For lipid metabolism, colorectal cancer cells can uptake CAF-synthesized fatty acids via CD36, and CAFs induce castration resistance in prostate cancer cells through elevating cholesterol and steroid biosynthesis.[18,19]

In this section, we dive into the mechanisms of restoring anti-tumor immune cell functions through tumor metabolic reprogramming in a hostile TME.

Deprivation of nutrients

Glucose

In the metabolic "tug-of-war" for key nutrients between tumor cells and immune cells, glucose is one of the most extensively studied nutrients (Fig. 2a). Glucose deprivation impairs the interferon-γ (IFN-γ) production of effector T cells (T_{effs}) and NK cells.[20,21] Besides, DCs need hyperactive glycolysis to initiate the stimulator of interferon genes (STING) pathway for type I interferon (IFN-I) secretion,[22] and it can be inferred that their anti-tumor immunity is attenuated when glucose is constrained. Glucose deprivation also hampers the anti-tumor immunity through altering an epigenetic landscape of T cells. Insufficient glucose promotes the expression of miRNA26a and miRNA101 in $CD8^+$ T cells to impair lysine 27 trimethylation on histone H3 (H3K27me3) via downregulating the enhancer of zeste homolog 2 (EZH2), ultimately hampering the production of IFN-γ and tumor necrosis factor (TNF).[23] This finding reveals the intricate link between metabolic profiles and epigenetic changes in reshaping immune response against tumors, and targeting EZH2 in CTLs could provide a novel insight into preventing tumor immune evasion.

Amino acids

Tumors consume a great amount of amino acids, and immune cells fail to perform their normal functions without adequate supply of these amino acids (Fig. 2a). Among these amino acids, glutamine, arginine, tryptophan and methionine are the most widely studied. Upon entry into cells, glutamine is involved in nucleotide biosynthesis, alternatively, it can be catabolized into glutamate and glutathione (GSH), which are responsible for energy production and redox balance, respectively. Thus, a deficiency in glutamine in the TME weakens $CD8^+$ T cell activation[24] and induces Treg differentiation, a major type of immune cells promoting immune evasion.[25] Inadequate glutamine also impairs T cell proliferation via inhibiting fatty acid synthesis (FAS) under hypoxic conditions.[26]

Due to downregulated expression of the enzymes for *de novo* synthesis of arginine including argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL),[27] tumor cells predominately uptake exogenous arginine. It has been reported that arginine is critical for survival of T cells *in vitro*,[6] and a deficiency in arginine

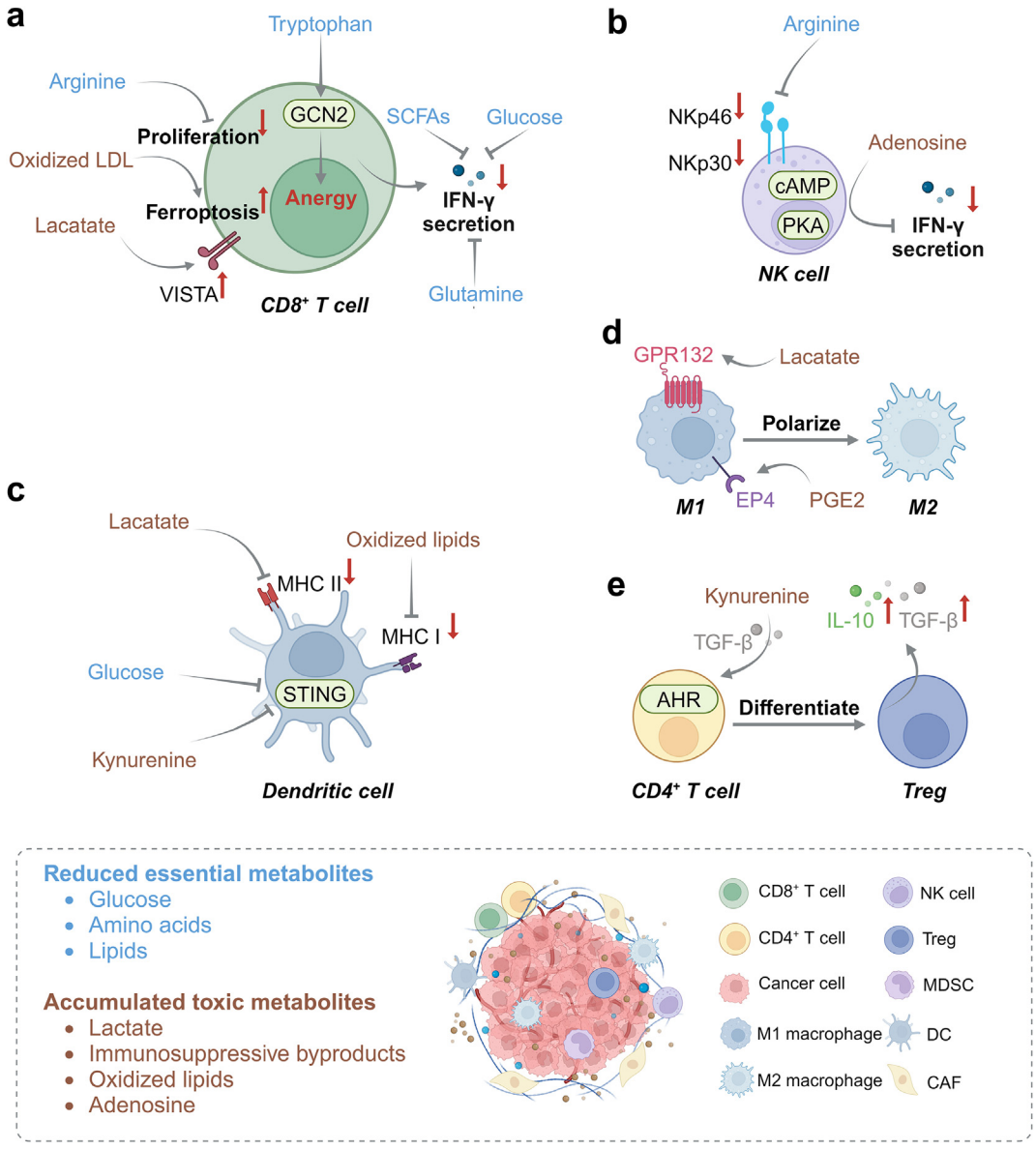

Fig. 1: **A hostile TME is characterized by nutrient deprivation and toxic metabolite accumulation**. (a) Deprivation of nutrients impairs the anti-tumor immune response of $CD8^+$ T cells: inadequate supply of glucose, glutamine and short-chain fatty acids (SCFAs) reduce IFN-γ secretion; inadequate supply of arginine leads to impaired proliferation; tryptophan deficiency induces anergy in $CD8^+$ T cells via activating general control nondepressible 2 (GCN2); accumulation of oxidized LDL induces ferroptosis in $CD8^+$ T cells; and accumulated lactate activates co-inhibitory receptor VISTA on $CD8^+$ T cells. (b) Arginine deficiency reduces NK cell viability via downregulating the expression of activating receptors including NK cell protein 30 (NKp30) and NKp46, and the accumulation of adenosine inhibits IFN-γ secretion of NK cells via upregulating the cAMP-PKA signaling pathway. (c) Excessive kynurenine and insufficient glucose inhibit STING pathway-mediated innate immunity in DCs; and the accumulated lactate and oxidized lipids impair antigen presentation via inhibiting the function of MHC II and MHC I, respectively. (d) A high level of lactate and PGE2 in the TME induces M1-to-M2 polarization of TAMs via GPR132 and EP4, respectively. (e) Kynurenine binds to the aryl hydrocarbon receptor (AHR) in $CD4^+$ T cells to induce their differentiation into Tregs in the presence of TGF-β, and Tregs excrete a large amount of immunosuppressive TGF-β and IL-10.

impairs their proliferation due to loss of cyclin D3 and cyclin-dependent kinase 4.[28] Besides, arginine is a substrate for the synthesis of NO, a pro-inflammatory cytokine, by M1 macrophages via NOS2, which facilitates tumor regression.[29] An arginine-deficient environment impairs the viability and proliferation of NK cells via inhibiting NKp30 and NKp46.[30] Therefore, inhibiting the arginine transporter[31] or directly depleting

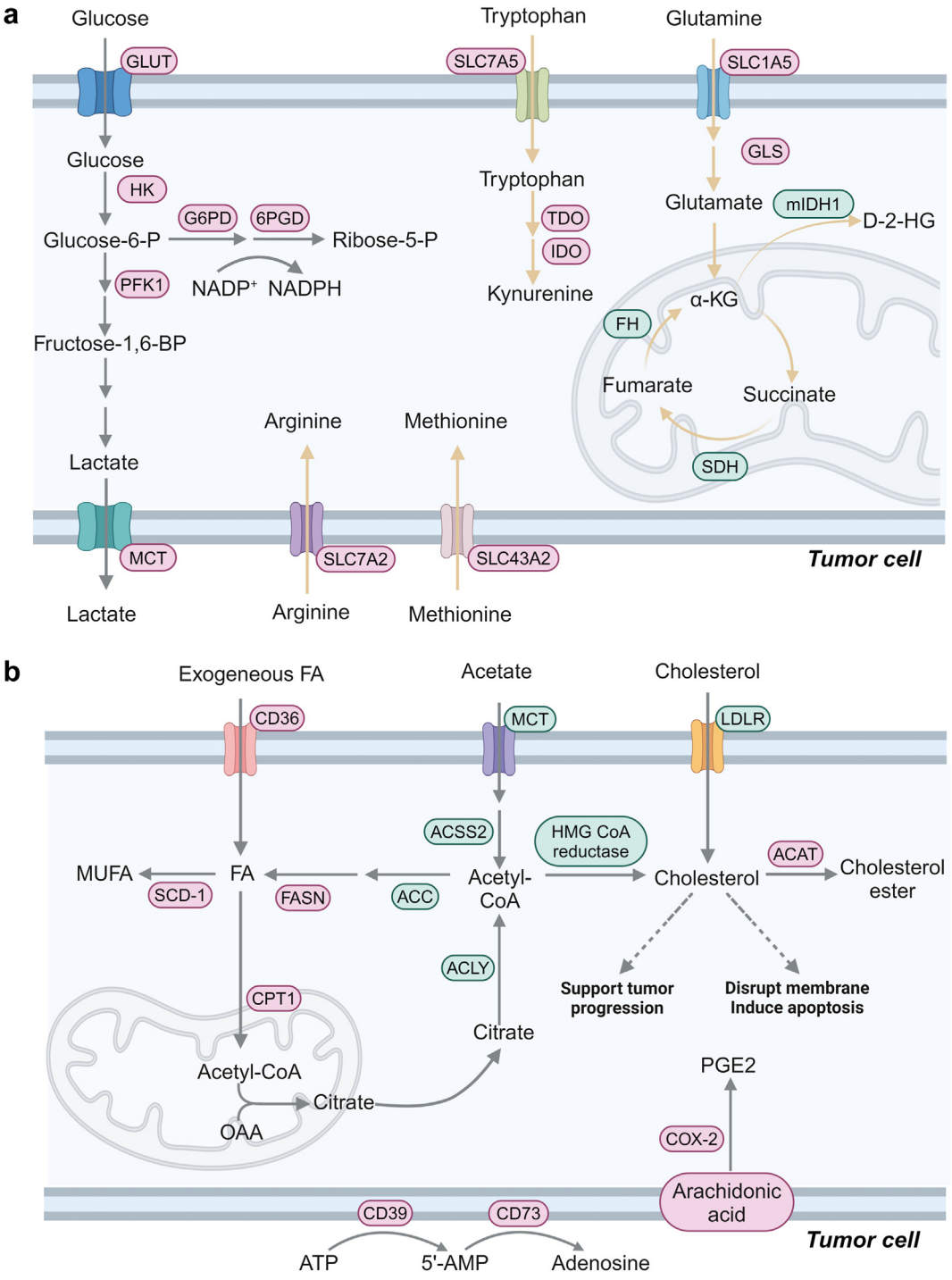

***Fig. 2:* Precisely reprogramming metabolism in tumor cells via nanomedicine**. (a) Cancer-promoting factors, such as MYC and hypoxia-inducible factor (HIF-1α), induce tumor cells to overexpress glucose transporter 1 (GLUT1), hexokinase (HK) and lactate dehydrogenase-A (LDH-A), leading to enhanced glucose uptake and lactate production. Besides, the pentose phosphate pathway (PPP) coordinates the modulation of tumor growth, and tumor cells upregulate the expression of glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) to maintain a high flux of PPP, which provides tumor cells with ribose-5-phosphate and reducing equivalent NADPH to support the biosynthesis of nucleotides and lipids. Glutamine can enter cells via SLC1A5, and it is catabolized to glutamate with the help of glutaminase (GLS) to enter the tricarboxylic acid (TCA) cycle for biosynthesis. Tumor cells usually express hypofunctional SDH and hyperactive mIDH1, leading to the accumulation of succinate and immunosuppressive D-2-HG, respectively. Tryptophan enters tumor cells via SLC7A5 and it

arginine[32] in arginine-dependent tumors could serve as a promising anti-cancer therapeutic approach.

Tryptophan deficiency induces T cell exhaustion through activating the general control non-depressible 2 (GCN2).[33] The upregulation of IDO in DCs can increase kynurenine production and induce Treg differentiation via the activation of AHR.[34] IDO-mediated tryptophan depletion can be rescued by tryptophan supplementation or IDO inhibition. Targeting IDO and/or TDO is able to increase the availability of tryptophan in the TME and revitalize CTLs to become functional against tumors.

Methionine is an important raw material for S-adenosyl-methionine (SAM), which is involved in the methylation of various nucleic acids and proteins. Deprivation of methionine induces apoptosis in $CD8^+$ T cells via inhibiting dimethylation of histone H3 at lysine 79 (H3K79me2), weakening the anti-tumor immunity.[35] Besides, a reduction in H3K79me2 increases PD-1 expression on $CD4^+$ T cells, which promotes tumor immune evasion.[36] The supplementation of SAM enhances the anti-PD-1 antibody efficacy via promoting the proliferation of $CD8^+$ T cells, and their production of IFN-γ and TNF-α.[37] These results suggest that blocking the methionine transporter SLC43A2 of tumors or specifically supplying methionine to T cells can enhance anti-tumor immunity and prevent metastasis.

Lipids

In addition to glucose and amino acid metabolism, lipid metabolic reprogramming in tumors attenuates anti-tumor immune response (Fig. 2b). Proliferating tumor cells usually upregulate FAS for cell membrane construction and energy production.[38] Tissue-resident memory T (Trm) cells rely on fatty acid oxidation (FAO) rather than glucose metabolism for their survival and biological functions. Trm cells are induced to death when they are co-cultured with gastric adenocarcinoma cells, which suggests that tumor cells outcompete Trm cells for securing fatty acids.[39] FAO can also increase the spare respiration capacity in $CD8^+$ memory T cells in response to stress, thus their long-term survival may be impaired under a lipid-deficiency environment.[40] Besides, gut microbiota-derived SCFAs are involved in modulating immune cell functions. Among them, pentanoate and butyrate have been shown to improve TNF-α and IFN-γ secretion of CTLs via inhibiting histone deacetylation of tumor suppressor genes[41] and promote antigen re-encounter response and long-term survival of $CD8^+$ T cells via fueling OXPHOS.[42] A comprehensive elucidation of the influence of microbiota ecology on immune cell metabolism in tumors could be harnessed to improve the anti-tumor immune effect.

Cancer cells are often in great demand of cholesterol. Tumor cells can synthesize a large quantity of cholesterol through the mevalonate pathway (MVA pathway) by up-regulation of sterol regulatory element binding proteins-2 (SREBP-2).[43] Apart from constituting cell membranes, cholesterol facilitates cancer stem cell renewal, promotes proliferation and induces drug resistance.[44] Therefore, tumors often have an insatiable appetite for cholesterol, while access to cholesterol by immune effector cells is restricted, which impairs anti-tumor immunity. For example, membrane cholesterol is essential for T cell receptor (TCR) clustering and immune synapse formation.[45] Besides, NK cells with abundant cholesterol-containing lipid rafts on the membrane exhibit enhanced anti-tumor activity.[46] Moreover, DCs that are deficient in cholesterol efflux promote pro-inflammatory T cell differentiation.[47] Interestingly, subcellular location of cholesterol in immune cells has a great impact on their functions, but its mechanistic details remain to be elucidated.

Immunosuppressive metabolites

Lactate

Lactate accumulation in the TME has been shown to be related to poor prognosis. The majority of lactate is exported by monocarboxylate transporter protein 4 (MCT4) to prevent acidosis. It is well accepted that lactate in an acidic TME impairs the function of T cells, specifically, an influx of a high concentration of lactate into T cells via MCT inhibits cellular glycolysis, preventing their activation and IFN-γ secretion.[48] In addition, an acidic environment can inhibit CTLs proliferation through promoting the binding of P-selectin glycoprotein ligand-1 (PSGL-1) to VISTA.[49] G-protein coupled receptor 81 (GPR81) is overexpressed on tumor cells, which can be activated upon binding to lactate, leading to angiogenesis, drug efflux and PD-L1 expression.[50] Additionally, GPR81 expression is

is catabolized to immunosuppressive kynurenine by IDO and TDO. Substantial arginine and methionine predominantly enter tumor cells via SLC7A2 and SLC43A2, respectively. (b) The building block for fatty acids is acetyl coenzyme A, which can be transformed from acetate and citrate by acetyl-coenzyme A synthetase 2 (ACSS2) and ATP-citrate lyase (ACLY), respectively. Catalyzed by Acetyl-CoA Carboxylase (ACC), acetyl coenzyme A is converted to malonyl coenzyme A, which is prolonged by fatty acid synthase (FASN) to form saturated fatty acids. Finally, saturated fatty acids are transformed to unsaturated ones with the help of stearoyl-CoA desaturase-1 (SCD-1). To maintain rapid proliferation, tumor cells uptake exogenous cholesterol via LDLR or synthesize ingenuous cholesterol, while an excessive level of cholesterol may induce tumor cell apoptosis. PGE2 is derived from arachidonic acid and it is predominately mediated by cyclooxygenase-2 (COX-2). Besides, adenosine is converted from ATP via CD39 and CD73. Targets in red texts are discussed in this review, while those in green texts remain to be elucidated. Solid arrows are used to indicate the process of metabolites from uptake to metabolic conversion by tumor cells; dashed arrows to introduce distinct roles of different cholesterol levels in tumor cells.

upregulated in DCs and lactate-GPR81 interaction inhibits the transfer of MHC II to the cell surface, ultimately impairing activation of T cells and promoting tumor immune evasion.[51] Lactate also induces the polarization of TAMs towards M2 via binding to GPR132 and promotes tumor metastasis.[52] Alleviating immunosuppressive effects of lactate in the TME can be achieved by breakdown of lactate or prevention of lactate production or efflux.

Intermediates in the TCA cycle

It has been demonstrated that intermediates in the TCA cycle also facilitate tumor immune evasion (Fig. 2a). The IFN-γ secretion of T cells is reduced in patients with pheochromocytoma and paraganglioma because a high extracellular succinate concentration disturbs their TCA metabolism.[53] In addition, D-2-HG alters glycolysis in $CD8^+$ T cells via an LDH inhibition-mediated decrease in the NAD^+/NADH ratio, ultimately leading to diminished IFN-γ production.[54] Encouragingly, L-2-HG, a D-2-HG isomer, boosts the tumor-killing ability of $CD8^+$ T cells when they are cultured *in vitro*, which may be attributed to the epigenetic modification effect of L-2-HG. To be specific, L-2-HG can inhibit H3K27me3 demethylation and promote CD62L transcription, and CD62L transcription is essential for central memory $CD8^+$ T cell differentiation.[55] Therefore, future efforts should be made into exploring the role of the two enantiomers of 2-HG in tumor immunity.

Kynurenine

Tumor cells usually overexpress IDO and TDO to consume tryptophan and produce immunosuppressive kynurenine, which inhibits anti-tumor immunity in an AHR-dependent manner. It has been demonstrated that CAFs can educate normal fibroblasts to upregulate their expression of IDO-1, which is similar to that in CAFs.[56] Through interaction with AHR, kynurenine can induce the differentiation of Tregs in the presence of transforming growth factor-β (TGF-β).[57] In addition, kynurenine can promote the production of IL-10 in NK cell and downregulate IFN-I response in DCs, thus supporting tumor immune evasion.[58,59] Blocking kynurenine-AHR engagement can reverse the suppressive activity of Tregs and TAM and enhance tumor-killing of $CD8^+$ T cells.[60] Accordingly, IDO inhibitors[61] and kynureninase[62] have been explored to reduce immunosuppressive kynurenine in the IDO-kynurenine-AHR signaling pathway.

Lipids and their derivatives

The accumulation of oxidized lipids in DCs has been shown to undermine their ability of antigen cross-presentation, in turn affecting CTLs activation, which may be due to the accumulation of peptide-MHC I complexes in lysosomes.[63] Besides, TAMs increase the uptake of lipids via CD36 from the TME for fatty acid oxidation (FAO) to initiate the JAK1-STAT6 signaling to achieve M2 polarization and promote tumor growth.[64] Therefore, targeting CD36 and/or FAO may become a new strategy of reprogramming TAMs for anti-tumor therapy. Oxidized lipids can stimulate the exhaustion of tumor-infiltrating T cells (TILs) since the uptake of oxidized low-density lipoproteins (oxLDLs) via CD36 leads to lipid peroxidation and a reduction in the production of IFN-γ and TNF.[65] Therefore, inhibition of CD36 and overexpression of glutathione peroxidase 4 (GPX4) can mitigate lipid peroxidation and restore anti-tumor immunity in TILs.

Overexpressed PD-L1 on tumor cells exhausts CTLs, leading to poor overall survival. Cholesterol can stabilize PD-L1 by binding to the transmembrane domain of PD-L1, suggesting that modulation of cholesterol metabolism may increase the efficacy of anti-PD-L1 antibodies.[66] 27-hydroxycholesterol has been found to inhibit SREBP-1 activation and interfere with glucose metabolism and secretion of IFN-γ by NK cells.[67] In addition, 22-hydroxycholesterol can recruit tumor-promoting neutrophils in a CXCR2-dependent manner for tumor angiogenesis, thus favoring tumor growth.[7] Overall, both oxidized lipids show a wide range of immunosuppressive properties.

Cyclooxygenase-2 (COX-2) is commonly overexpressed in a wide range of tumor tissues, producing abundant immunosuppressive PGE2 to promote tumor progression via MDSCs and Tregs (Fig. 2b). PGE2 potentiates MDSCs to induce immunosuppressive IL-10 production by Tregs.[8] Meanwhile, PGE2 can induce arginase 1 (ARG1) expression via E prostanoid 4 receptor (EP4) in MDSCs to deplete arginine for T cells, thus resulting in a less potent anti-tumor effect in the TME.[68] Through binding to EP2 and EP4, PGE2 not only diminishes the cytotoxicity of NK cells and γδ T cells via the cAMP-PKA signaling pathway,[69] but also enhances the recruitment of Tregs by mature regulatory DCs via secreting CCL17 and CCL22.[70] In addition, PGE2 is involved in the regulation of macrophage polarization from M1 phenotype to pro-tumor M2 phenotype, reducing the release of TNF-α and IL-12.[71] Considering a high expression level of COX-2 in tumor tissues, a reduction in immunosuppressive PGE2 production could be realized by inhibiting COX-2 or blocking PGE2 receptors via nanomedicine.

Adenosine

ATP can be released to the extracellular matrix in response to cellular stress and it is sequentially converted to 5′-AMP and adenosine predominately by extracellular nucleotidases including CD39 and CD73 (Fig. 2b). Excessive extracellular 5′-AMP blocks the differentiation of MDSCs into DCs.[72] Interestingly, the interaction between CAFs and TILs accelerates adenosine production: TILs upregulate the CD73 expression on CAFs, and in turn CAFs promote CD39 expression

on TILs.[73] The overexpression of CD39 and CD73 on tumor cells, tumor-derived exosomes, Tregs,[74] CAFs and TILs synchronizes to produce excessive adenosine, which promotes tumor immune evasion through interacting mainly with adenosine receptors A2AR and A2BR. A great amount of adenosine inhibits the IFN-γ secretion of CTLs via A2AR.[9] Notably, hypoxia and HIF-1α upregulate the expression of the A2BR in DCs as well as inhibit their antigen uptake and migration, ultimately weakening the activation of CTLs. It is noted that adenosine directs the differentiation of monocytes into M2 macrophages upon binding to A2BR.[75] These results suggest that antagonists of CD39, CD73, and adenosine receptors can remodel the TME to alleviate tumor immune evasion.

Nanomedicine improves the TME via metabolic reprogramming

Since tumor cells uptake and catabolize abundant nutrients through overexpressing their transporters and enzymes, as well as excrete a myriad of immunosuppressive metabolites, modulation of essential nodes in the metabolism of tumor cells could ameliorate the hostile TME to some extent. Besides, modulation of the metabolism in immune cells and CAFs can further enhance anti-tumor immunity. However, the use of metabolism-modulating agents faces challenges because of their severe toxicity due to their off-target effects and poor bioavailability. The application of nanomedicine can realize the delivery of metabolic regulators to the target cell types. On the one hand, nanoparticles can passively accumulate in tumor sites through the enhanced permeability and retention (EPR) effect. On the other hand, specific ligand-modified nanoparticles can actively conjugate to the targeted cells through ligand–receptor interactions. For example, 2-Deoxyglucose (2-DG), a glucose mimetic drug, inhibits glycolysis in tumor cells while induces inevitable cardiotoxicity,[76] but tumor cell-targeting 2-DG nanovesicles could eliminate lung cancer cells and reveals no significant damage to major organs 14 days posttreatment.[77] Overall, nanomedicine-aided metabolic reprogramming of the TME has great potential to augment the efficacy and safety of immunometabolism-modulating agents.

The mainstream flow: targeting tumor cells

The progress in the field of immunometabolism has revolutionized immunotherapy, and the vast majority of immunometabolic strategies are devoted to modulating the metabolism of tumor cells. Nanomedicine has been applied to reprogram the metabolism of tumor cells through various approaches: (1) blocking glycolysis and preventing lactate production via inhibiting HK2, phosphofructokinase (PFK), LDHA, GLUT1 and MCT4[78–83]; (2) decreasing NADPH production via inhibiting G6PD and 6PGD[84,85]; (3) restricting glutamine metabolism via GLS inhibitors, 6-Diazo-5-oxo-L-norleucine (DON) and SLC1A5 blockade[86–88]; (4) decreasing arginine uptake via SLC7A2 blockade and depleting arginine via arginine deiminase[31,32,89]; (5) interfering with tryptophan metabolism via IDO inhibitors and kynureninase[61,90]; (6) inhibiting methionine uptake via genetic knockout of SLC43A2[91]; (7) interfering with fatty acid and cholesterol metabolism via downregulating the expression of FASN, SCD-1 and CD36[92–96]; (8) decreasing immunosuppressive PGE2 production via downregulating HIF-1α[97,98]; (9) reducing the production of adenosine via inhibiting CD39 and CD73[99] (Supplementary Tables S1–S5). Details on reprogramming the metabolism of tumor cells via nanomedicine can be seen in Supplementary Material.

A breath of fresh air: targeting tumor-suppressing immune cells

We have discussed advances in reprogramming tumor metabolic pathways to ameliorate the immunosuppressive TME, but the immune-modulatory effect is often indirectly induced through the ICD effect. Since immune cells are one of the critical components in the TME, the modulation of an immunosuppressive TME could be realized via targeting immune cells in the TME.[100,101] There are very few reports on nanomedicine-mediated metabolic reprogramming of immune cells. Herein, we will cover current advances in using nanomedicine for metabolic reprogramming in immune cells in the TME.

A tumor–immunity cycle typically begins with the release of antigens after triggering tumor cell death from therapeutic treatment. Immature DCs can uptake and process these antigens, and they become mature. Mature DCs activate T cells via antigen presentation in tumor-draining lymph nodes (TDLNs). The activated T cells infiltrate to tumor sites via the vascular system. CTLs are the most effective anti-tumor immune cells via secreting IFN-γ, granzyme B and the Fas/FasL pathway. The release of antigens from fresh dead tumor cells allows the tumor–immunity cycle to continue sustainably[102] (Fig. 3a). However, there remain various metabolic barriers to this cycle in the TME. For example, glucose shortage affects the infiltration of CTLs and their anti-tumor effects[48]; excessive lipid accumulation in the TME impairs antigen processing and presentation of DCs.[103] Strategies have been developed for metabolic rewiring in DCs and T cells via nanomedicine, especially surface-engineering of T cells is very promising in promoting anti-tumor immunity (Supplementary Table S6).

Enhancing antigen presentation by DCs

Glycolysis is essential for both activation of DCs, which mediate T cell activation. Instead of complex genetic upregulation of glucose transporters and glycolysis

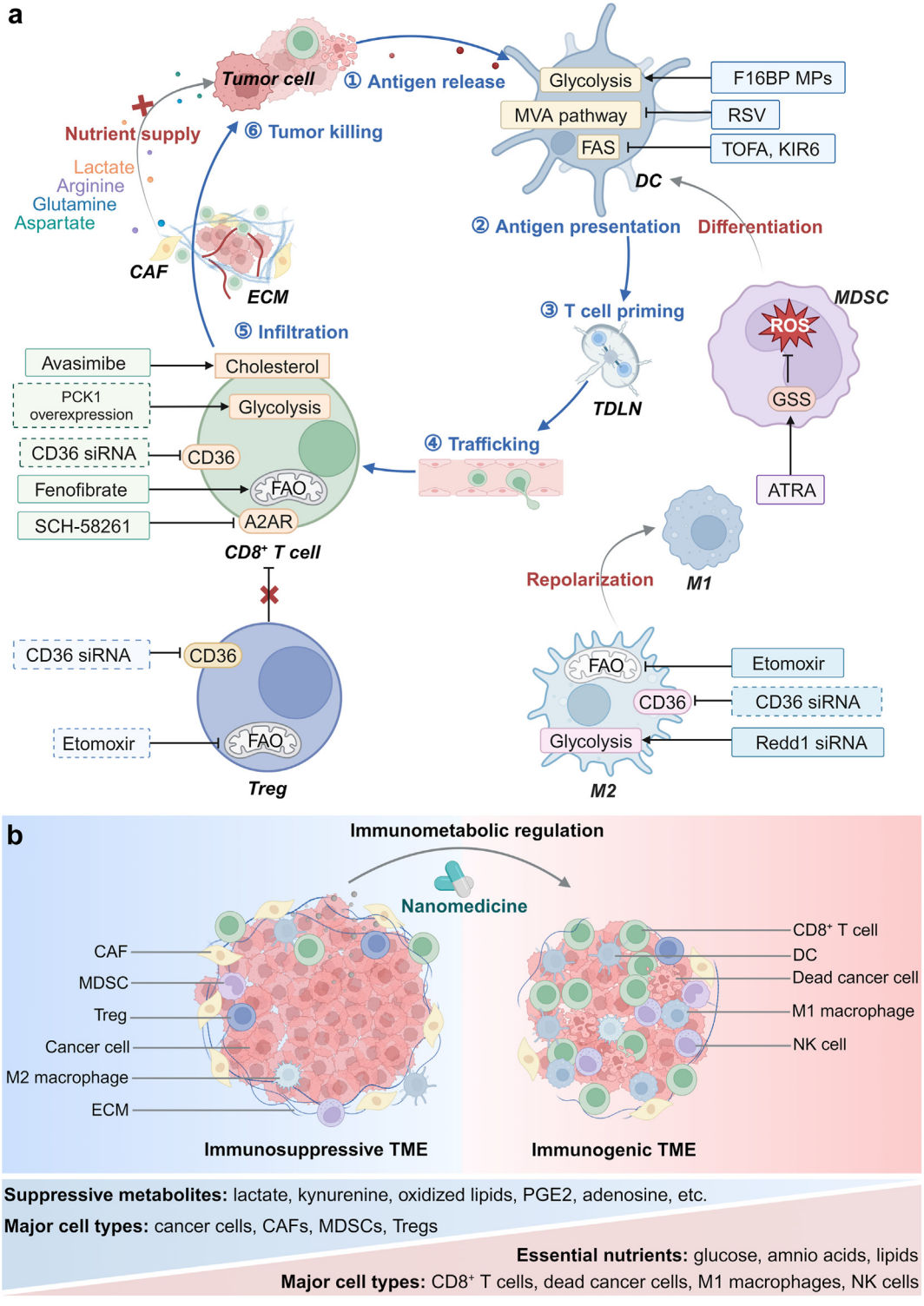

***Fig. 3:* Overview of metabolic reprogramming of immune cells and CAFs via nanomedicine.** (a) Schematic illustration of a tumor–immunity cycle including the following steps: antigen release, antigen presentation, T cell priming, $CD8^+$ T cell trafficking through the vascular system, infiltration into deep tumor tissues, and tumor killing. Several targets have been identified to remodel an immunosuppressive TME via modulating metabolic pathways in cancer cells, CAFs and immune cells: (1) nanomedicine-based metabolic reprogramming strategies help restoring the proliferation of $CD8^+$ T cells and their secretion of effector cytokines, and facilitating antigen-presentation by DCs; (2) MDSCs and

enzymes in DCs, directly replenishing glycolytic ingredients to DCs may be an effective and feasible approach. Inamdar et al. formulated F-1,6-BP microparticles (F16BP MPs), which contained an immune adjuvant and melanoma cell antigens. These microparticles were phagocytosed by DCs, rescuing glycolysis and activation of DCs after systemic administration of PFK15, a glycolysis inhibitor. Encouragingly, treatment with F16BP MPs elevated CTL/Treg ratio, ultimately promoting immune response against melanoma.[104] The strategy realized specific inhibition of glycolysis in tumor cells and replenished substrates for DC-targeting glycolysis, thus efficiently activating anti-tumor immunity. Through the same approach, exhausted T cells in the TME can be rescued via targeted delivery of critical substrates.

Furthermore, abnormal lipid metabolism has a negative impact on antigen cross-presentation in DCs and priming of T cells. 5-tetradecyloxy-2-furoic acid (TOFA) is often used to block FAS via inhibiting ACC, but its poor aqueous solubility and bioavailability diminish its efficacy via an oral administration route. Recently, Qin et al. constructed a lipid metabolism-manipulating nanovaccine, TPOP, which was comprised of TOFA-loaded PLGA nanoparticles coated with bacteria outer membranes. Pathogen-associated molecular patterns on the bacteria outer membrane can be recognized by pattern recognition receptors on DCs, thus TPOP was successfully phagocytosed by DCs. Therefore, the TPOP nanovaccine could specifically target DCs. After administration of doxorubicin (DOX) and TPOP, DOX induced the ICD effect to release tumor-associated antigens, which were captured by the TPOP nanovaccine via the Michael addition reaction. Uptake of the TPOP nanovaccine by DCs decreased in the intracellular level of triglyceride and cholesterol ester, and promoted maturation and antigen presentation of DCs. Consequently, the TPOP nanovaccine helped increasing the level of anti-tumor cytokines and the population of effector memory T cells, thus effectively suppressing the primary tumor and distant lesions in B16F10 tumor-bearing mice[103] (Supplementary Figure S1). This suggests that normalization of FAS is essential for antigen cross-presentation of DCs, which facilitates restoring the weakened anti-tumor immunity.

In line with excessive fatty acids accumulation, abnormal cholesterol metabolism also exerts a negative impact on antigen cross-presentation by DCs. Specifically, the activity in the MVA pathway of tumor-infiltrating DCs is upregulated, and its downstream metabolite, geranylgeranyl diphosphate (GGPP), can activate GTPase Rab5 to induce antigen degradation by lysosomes, thus impairing the ability of antigen cross-presentation of DCs.[105] Rosuvastatin (RSV), an inhibitor for the MVA pathway, has been widely used to decrease the plasma cholesterol level in clinical practices. To realize precise and long-term modulation of cholesterol metabolism in DCs, Yang et al. developed a mannose-decorated hydrogel delivery system to load RSV to construct Gel@NPs. After binding to overexpressed mannose receptors on DCs, Gel@NPs were specifically internalized by DCs. RSV was released sustainably to reactivate antigen cross-presentation of DCs and strengthen tumor-killing of CTLs, thus forming an immunocompetent TME[106] (Supplementary Figure S1). This result implies that nanomedicine-assisted metabolic modulation could enhance activation and antigen presentation of DCs in the TME, thus activating the anti-tumor immunity.

Revitalizing tumor-suppressive effects of T cells

A hypoglycemic TME often exhausts T cells through interfering with aerobic glycolysis which is essential for IFN-γ secretion and proliferation.[48] It has been found that phosphoenolpyruvate (PEP) can promote activation of T cells and enhance production of cytotoxic effector molecules.[107] Therefore, overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1), which produces PEP from oxaloacetate (OAA), can enhance anti-tumor effects of T cells. However, the challenging issue is to achieve specific overexpression of PCK1 in TILs, but not in tumor cells. T cells-targeting nanomedicine might be employed to specifically upregulate PCK1 in TILs.

In addition, $CD8^+$ T cells maintain their anti-tumor ability under a glucose-deprived condition via upregulating peroxisome proliferators-activated receptor-α (PPAR-α) and FAO.[108] To selectively deliver fenofibrate, an agonist of PPAR-α, to T cells, Kim et al. encapsulated fenofibrate into anti-CD3e f (ab')2 fragment-modified amphiphilic polygamma glutamic acid-based nanoparticles (aCD3/F/ANs). It was demonstrated that aCD3/F/ANs were specifically uptaken by $CD3^+$ T cells. Through activating PPAR-α, aCD3/F/ANs promoted FAO in T cell mitochondria via upregulating expression of the related enzymes and transporters. This nanomedicine increased tumor-infiltrating $CD8^+$ T cell proliferation and enhanced their cytokine production, effectively inhibiting B16F10 tumor growth[109] (Fig. 4). The result indicates that mitochondria are essential for augmenting the T cell function and reprogramming

M2 macrophages can be transformed to mature DCs and M1 macrophages via nanomedicine-assisted metabolic modulation, respectively; (3) metabolic reprogramming of Tregs via nanomedicine can attenuate their suppressive activity; and (4) regulating glycolysis and amino acid metabolism in CAFs can block their nutrient supply to tumor cells. Well-established targets are shown in solid boxes, while targets that remain to be explored are in dashed boxes. (b) Nanomedicine-aided immunotherapy can reverse an immunosuppressive TME to an immunogenic one via immunometabolic regulation.

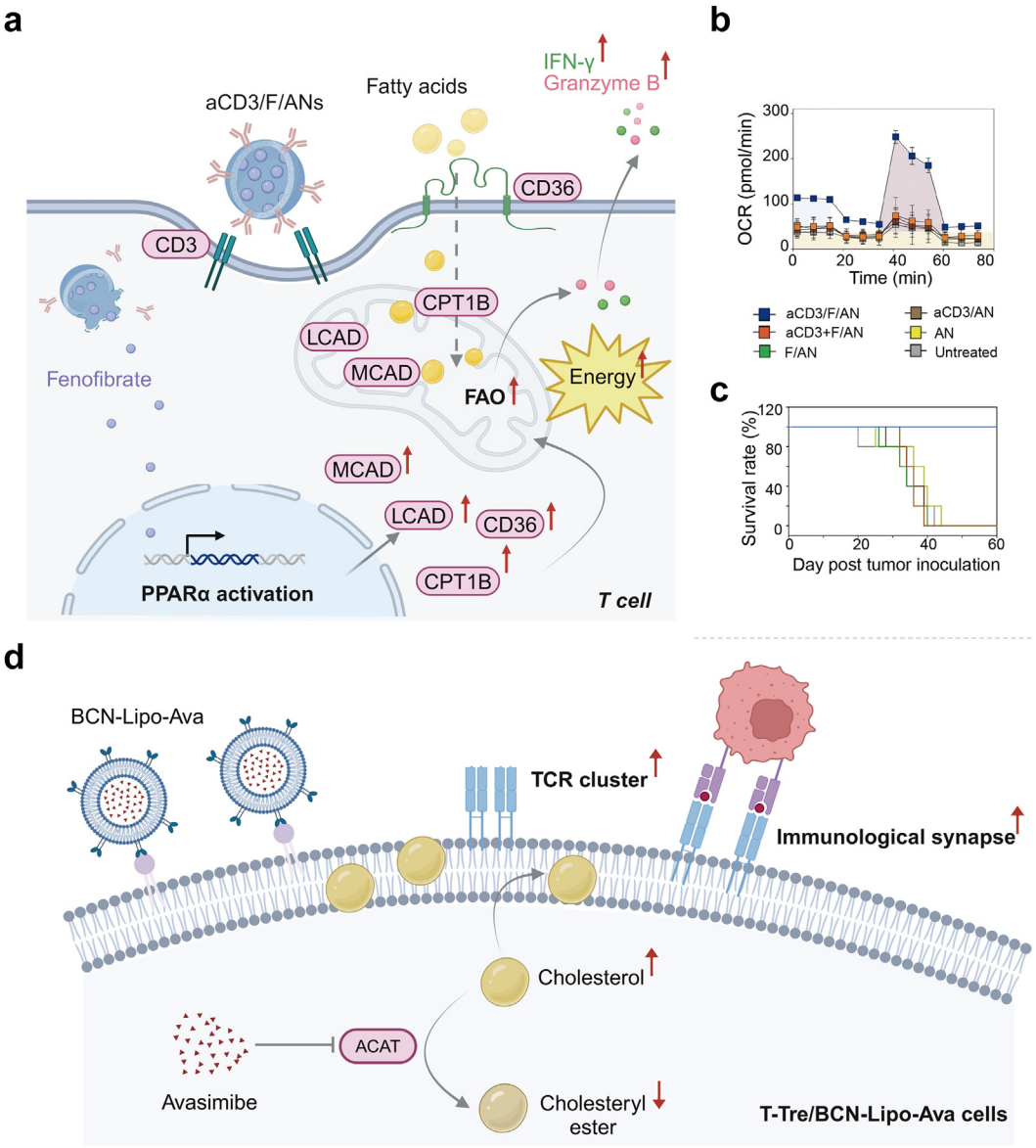

Fig. 4: **Precisely reprogramming FAO and cholesterol metabolism in T cells via nanomedicine**. (a) Scheme for aCD3/F/ANs to reprogram FAO in T cells via upregulating the expression of CD36, CPT1B, long chain acyl-CoA dehydrogenase (LCAD) and medium chain acyl-CoA dehydrogenase (MCAD), leading to an elevation in the secretion level of IFN-γ and granzyme β. OCR (b) and survival rate (c) of the aCD3/F/ANs-treated group compared to those from other treatment groups. Reprinted with permission from ref.[109] Copyright 2021 Springer Nature. (d) Schematic illustration of the mechanism for an enhancement in anti-tumor response of T-Tre/BCN-Lipo-Ava cells.

lipid metabolism in adoptive T cells may enhance their survival and anti-tumor effects.

A high level of cholesterol in the plasma membrane is positively correlated with the tumor-killing ability of $CD8^+$ T cells.[45] Compared with free avasimibe, Hao et al. innovatively anchored liposomes that contained avasimibe onto the membrane of T cells, then constructed T-Tre/BCN-Lipo-Ava cells without any impact on the physiology of T cells. The liposomal avasimibe was stably attached to the cell surface for up to 4 days and avasimibe was sustainably released to increase the membrane cholesterol concentration. The surface-engineered T cells exhibited enhanced TCR clustering and immunological synapse maturation, which promoted anti-tumor cytokines secretion and boosted the tumor-killing capacity both in B16F10 and LN-299 tumor-bearing mice[110] (Fig. 4). This elegant method circumvents targeted delivery of metabolic modulators to T cells via nanoparticles, since vasculature extravasation of these nanoparticles is often hindered by a high

interstitial fluid pressure in the hostile TME. Enhancing anti-tumor activity of adoptive T cells by anchoring essential nutrients onto the immune cell surface via nanotechnology is a feasible approach, but side effects like the cytokine storm must be thoroughly examined before clinical translation.

Accumulation of adenosine in the TME suppresses various immune effector cells through ligation with A2AR. Masjedi et al. fabricated A2AR siRNA-loaded nanoparticles to downregulate the expression of A2AR in T cells, which relieved adenosine-mediated immunosuppression, enhanced the DCs vaccination efficacy, and increased $CD8^+$ T cell infiltration.[111] However, the delivery of nanomedicine into immune cells is often hindered by a hostile TME. A2AR antagonist SCH-58261 (SCH)-loading multilamellar liposomes, cMLVs, were constructed by Siriwon et al. and cMLVs were coupled onto the membrane of CAR-T cells, without affecting CAR-T cell function. The engineered CAR-T cells can effectively infiltrate into tumor sites via responding to chemoattractant gradients. Encouragingly, due to blockade of A2AR, the surface-engineered CAR-T cells recovered their tumor-killing potency and inhibited SKOV3 tumor growth. Unfortunately, IFN-γ secretion by the surface-engineered CAR-T cells was less than that of counterparts from healthy mice, indicating there were other immunosuppressive mechanisms.[112] Conjugation of multiple metabolic modulators to the membrane of engineered T cells has the potential to improve the anti-tumor immunity, while such a complex procedure for surface engineering of T cells may be very challenging for translation into clinical practice.

Notably, $CD4^+$ T cells can promote $CD8^+$ T cell anti-tumor immunity. Th_1 cell infiltration is a positive prognostic indicator in esophageal squamous cell carcinoma patients, since Th_1 cells can secrete IFN-γ, which improves antigen presentation via upregulating MHC II expression on DCs.[113] Th_1 cells are involved in $CD8^+$ T cell proliferation, recruitment and memory response.[114] Besides, Th_1 cells exhibit cytotoxicity independently of CTLs. Tumor cells often downregulate MHC I expression to evade CTL recognition while Th_1 cell produce IFN-γ to induce MHC II expression on tumor cells for recognition and secrete granzyme B to kill them.[115] Therefore, Th_1 cell may become a novel target for metabolic-reprogramming nanomedicine to enhance the anti-tumor response.

These results have suggested that nanomedicine-aided metabolic reprogramming of T cells could resolve the issues associated with direct administration of small molecular agents, particularly, nanomedicine can enhance their T cell-targeting ability, thus revitalizing exhausted T cells in the TME.

Make a friend out of an enemy: targeting tumor-promoting immune cells

Low immune response of immunotherapy may be stemmed from the presence of a substantial number of immunosuppressive cells (MDSCs and Tregs) and other immune cells (Th_{17} cells and TAMs) which exhibit paradoxical roles in promotion of tumor progression or inhibition of tumor growth. For example, Th_{17} cells are shown to promote anti-tumor immunity via inducing infiltration of DCs and CTLs into tumor sites, while Th_{17} cells can overexpress CD39 and CD73 to produce immunosuppressive adenosine in the presence of TGF-β.[116] In this section, we will elaborate the metabolic plasticity of MDSCs, TAMs and Th_{17} cells, and summarize recent advances in metabolic regulation of these cells via nanomedicine to amplify anti-tumor immunity.

Repolarizing TAMs to immunocompetent M1 phenotype

Tumors usually recruit circulating monocytes via secreting chemokine CCL2, and these monocytes are then differentiated into macrophages in the TME. The macrophages are referred to TAMs.[117] TAMs can be classified into M1 and M2 phenotypes, depending on their anti-tumor or pro-tumor role, respectively. Anti-tumor M1 macrophages primarily perform glycolysis for energy supply, while M2 macrophages, the predominant type of TAMs, prefer to mitochondria-mediated OXPHOS and FAO for energy production. Pro-tumor M2 macrophages weaken the antigen presentation by DCs via secreting IL-10 and TGF-β, and upregulate ARG1 expression to exhaust T cells.[118]

Repolarizing macrophages (M2 to M1) can significantly activate anti-tumor immune response (Supplementary Table S6). Since OXPHOS heavily depends on intact mitochondria, disruption of the mitochondrial activity could shift the metabolism from OXPHOS to glycolysis, promoting M1 repolarization. RSL3 can sensitize lipid peroxidation and ferroptosis via inhibiting GPX4. Thus, Gu et al. constructed an iron-based metal organic framework with the Fenton activity to realize metabolic conversion in TAMs. Fe-metal organic framework nanoparticles (MIL88B) were employed to load hydrophobic RSL3 to yield MIL88B/RSL3. The nanomedicine promoted lipid peroxidation on mitochondrial membranes, resulting in a shift in the energy production from OXPHOS to glycolysis, and ultimately M1 repolarization of TAMs. M1 macrophages generated via induction of MIL88B/RSL3 exhibited an enhancement in phagocytic killing, thus inhibiting 4T1 tumor growth.[119] However, the nanosystem was not equipped with the M2 macrophage-targeting ability.

It is desirable to increase the glycolysis level in M2 microphages instead of tumor cells. Knockdown of Redd1 can upregulate the glycolysis level through activating the mTOR pathway, thus promoting repolarization of M2 macrophages towards M1. Guo et al. loaded Redd1 siRNA into bacterial outer membrane vesicles (OMVs), and the nanovesicles were then modified with mannose and paclitaxel (PTX) to formulate siRNA@M-/PTX-CA-OMVs. Through the EPR effect, siRNA@M-/PTX-CA-OMVs accumulated in acidic tumor tissues and

released PTX to induce the ICD effect. Specific binding of the nanovesicles onto M2 macrophages was realized through interaction between CD206 on M2 macrophages and mannose on the nanovesicles. The knockdown of Redd1 via Redd1 siRNA in nanovesicles selectively promoted glycolysis in M2 macrophages and repolarized them towards M1. Besides, the nanovesicles helped increasing the number of TILs and effector cytokines levels, ameliorating the TME and inhibiting 4T1 tumor progression[120] (Supplementary Figure S2).

Interestingly, it has been found that tumor-derived long-chain fatty acids (LCFAs) are preferentially internalized by metastasis-associated macrophages via CD36, which drives their polarization towards M2, leading to a metastasis-promoting TME.[121] Therefore, nanomedicine-aided CD36 inhibition in TAMs may provide a prospective approach of repolarization of M2 macrophages towards their M1 phenotype. To conclude, nanomedicine-mediated metabolic reprogramming in TAMs has been demonstrated to remodel an immunosuppressive TME. The abundant TAMs assist in tumor progression; thus efforts should be made into exploring unveiled metabolic regulators for re-educating TAMs to the M1 phenotype for enhancing anti-tumor immunity.

Promoting the differentiation of MDSCs into DCs

MDSCs are a major type of immunosuppressive cells originated from hematopoietic stem cells and they can be differentiated into macrophages, DCs, and granulocytes. However, the TME prevents MDSCs differentiation, and immature heterogeneous MDSCs exhibit potent immunosuppressive properties. For example, MDSCs can overexpress ARG1 and NOS2. ARG1 could deplete arginine and impair T cell activation, and NOS2 produces NO to promote tumor angiogenesis through upregulating VEGF expression. In addition, PD-L1 expression and TGF-β secretion are enhanced in MDSCs, and a high level of ROS is produced, thus exhausting $CD8^+$ T cells.[122]

Notably, MDSCs have metabolic plasticity, which provides a foundation for differentiating immature MDSCs into mature cells via metabolic reprogramming. ATRA has been reported to induce the differentiation of MDSCs into mature macrophages and DCs through upregulating the expression of glutathione synthase (GSS) to synthesize GSH for scavenging ROS.[5,123] Zheng et al. constructed ATRA-encapsulated liposomes (L-ATRA) to significantly improve the solubility and the encapsulation efficiency of ARTA. L-ATRA effectively promoted MDSC differentiation into mature DCs and enhanced their expression of MHC II, thus improving the viability of $CD8^+$ T cells.[124] Therefore, nanoplatforms for ROS-scavenging and antioxidation may be used to promote differentiation of MDSCs into mature DCs and ameliorate an immunosuppressive TME.[125] Additionally, it has been reported that proliferation and suppressive activities of MDSCs are predominantly prompted by HIF-1α-driven glycolysis,[126] and tumor-infiltrating MDSCs exhibit a higher FAO level than their splenic counterparts in tumor-bearing mice.[127] Therefore, inhibition of glycolysis and FAO in MDSCs may alter their immunosuppressive properties. It is noted that these strategies have been reported to be feasible for tumor cells. Since different subsets of MDSCs are featured with distinct metabolic pathways, the interference with the metabolism in MDSCs to ameliorate an immunosuppressive TME remains to be elucidated.

Modulating the Th17/Treg axis to augment anti-tumor immunity

$CD8^+$ CTLs are the major type of effector cells in immunotherapy, whereas $CD4^+$ T cells including Th_{17}, Th_1, Th_2, and Tregs are involved in immunomodulation predominantly through the secretion of cytokines. Notably, Th_{17} cells exhibit environmentally-dependent plasticity,[128] indicating that they can be transformed into other types of $CD4^+$ T cells, primarily including anti-tumor Th_1 cells and pro-tumor Tregs, which lays the groundwork for the following discussion.

Th_{17} cells are featured with the production of IL-17, and Th_{17} cells have been shown to have a contradictory influence on tumor development. For example, Th_{17} cells can express CD39 and CD73 to produce immunosuppressive adenosine by decomposing the extracellular ATP[116] but produces IL-17 to recruit DCs to TDLNs for $CD8^+$ T cell activation.[129] IL-17 can facilitate tumor cell renewal,[130] and upregulate the expression of VEGF and CD31 to promote tumor angiogenesis,[131] but IL-17 level is positively associated with the prognosis of cervical adenocarcinoma.[132]

Tregs can express an array of immune checkpoints such as CTLA4, which can downregulate CD80 and CD86 on DCs to weaken their immunostimulatory ability.[133] In addition, Tregs induce the production of immunosuppressive adenosine to promote tumor immune evasion.[74] Therefore, we suggest that an elevation in the Th_{17}/Treg ratio may be beneficial for anti-tumor immunity.

It has been found that activation and proliferation of Th_{17} cells are dependent on glycolysis and FAS,[134] but Tregs are predominantly driven by OXPHOS and FAO from tumor-derived lactate and free fatty acids.[135] It is noteworthy that the trans-differentiation of Th_{17} cells to Tregs is promoted under the suppression of glycolysis in Th_{17} cells and the presence of PGE2.[136] Therefore, inhibition of COX-2 could reduce trans-differentiation of Th_{17} cells into pro-tumor Tregs, which could be realized through nanomedicine with precise targeting and efficient drug delivery capabilities.

Blocking metabolic crosstalk between tumor cells and CAFs

CAF-derived critical nutrients can be utilized by tumor cells, which is one of the latest pro-tumor mechanisms.

Therefore, nanomedicine-aided metabolic regulation of CAFs could help reducing the production of these nutrients, starving tumor cells to inhibit tumor growth (Supplementary Table S7).

Cancer cells and CAFs outcompete immune effector cells in gaining glucose via hyperactive glycolysis to produce lactate, which also promotes tumor immune evasion. To kill two birds with one stone, Zang et al. constructed homologous targeting nanoparticles, PTX/PFK15-SLN@[4T1-3T3] NPs, by co-loading PTX and PFK15 (a glycolysis inhibitor) onto solid lipid nanoparticles camouflaged with hybrid membranes from tumor cells and fibroblasts. Through the EPR effect, PTX/PFK15-SLN@[4T1-3T3] NPs were readily internalized by tumor cells and CAFs, inhibiting glycolysis and reducing lactate production in both cells. It is noted that glycolysis inhibition and reduced lactate production can starve tumor cells and attenuate lactate-mediated immunosuppression. Therefore, treatment with these nanoparticles increased $CD8^+$ T cell infiltration, enhanced effector cytokine secretion, and repolarized M2 macrophages towards M1, thus reshaping the immunosuppressive TME.[137] This strategy of targeting both tumor cells and CAFs to inhibit their glycolysis and attenuate lactate-mediated immunosuppression could be very effective in revitalize anti-tumor immunity.

CAFs are often stimulated to synthesize glutamine from tumor cell-derived glutamate via glutamate ammonia ligase (GLUL) to meet a high demand for glutamine by tumor cells.[14] To block the glutamine–glutamate cycle, Ai et al. constructed FH peptide-conjugated nanodroplets to co-load V9302 and siGLUL, resulting in FH-V9302-siGLUL-NDs. The nanodroplets exhibited a negligible hemolysis rate compared to free V9302. Since FH peptides have high affinity to overexpressed tenascin C on CAFs, FH-V9302-siGLUL-NDs could precisely target CAFs (Fig. 5). Both V9302 and siGLUL were rapidly released in a CAF-enriched TME under ultrasound irradiation to simultaneously downregulate the GLUL expression in CAFs and the SLC1A5 expression on tumor cells, inhibiting melanoma tumor growth and ECM deposition.[138]

Considering that CAFs are the main contributors to a dense ECM, which blocks the intratumoral penetration of nanodrugs and the infiltration of T cells, leading to unsatisfactory nanomedicine-mediated immunotherapy outcomes. It was reported that dendritic polymer-based sequential delivery of dasatinib and epirubicin exhibited great inhibition of collagen biosynthesis in CAFs by downregulating amino acid metabolism and energy production, resulting in an increased level of CTL infiltration[139] (Fig. 5). Although rewriting the

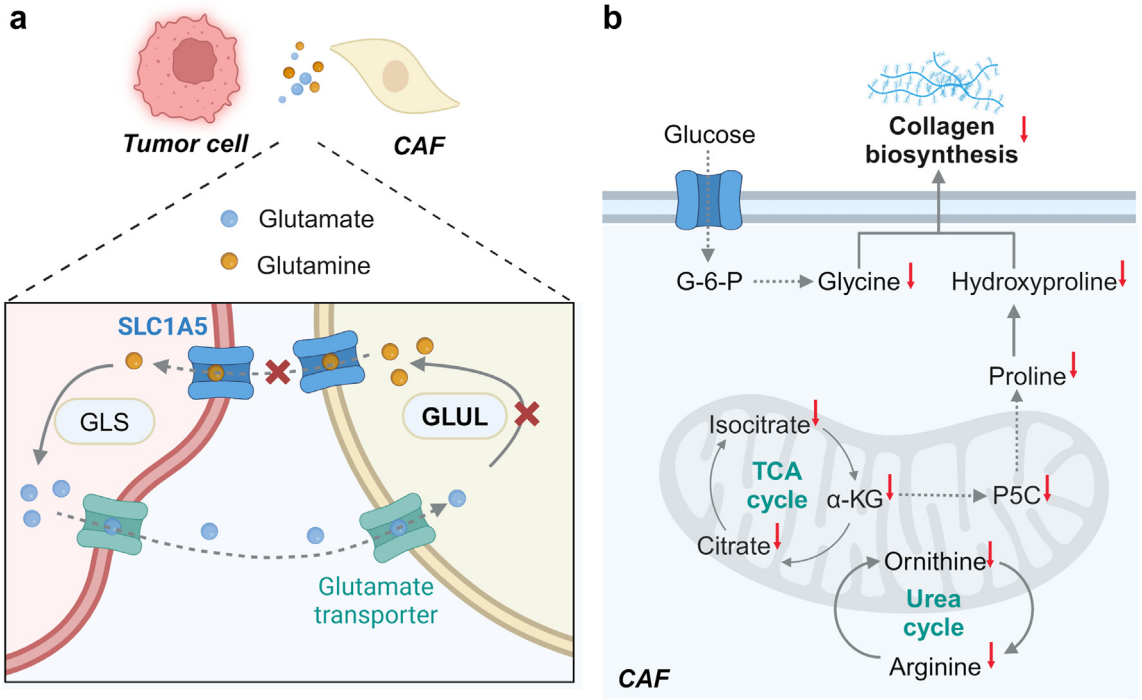

Fig. 5: **Nanomedicine-aided precise metabolic reprogramming of CAFs**. (a) Schematic illustration of FH-V9302-siGLUL-NDs to interfere with glutamine metabolic crosstalk between CAFs and tumor cells via blocking SLC1A5 and GLUL. (b) The mechanism of reducing collagen biosynthesis in CAFs by P-DAS via sequentially delivering dasatinib and epirubicin into CAFS to interfere with glycolysis and amino acid metabolism.

Search strategy and selection criteria

We searched the databases of PubMed for relevant articles published only in English, using the search terms "immune evasion", "immunotherapy", "metabolism", "tumor microenvironment", "nanomedicine", "glucose" or "lactate" or "glutamine" or "arginine" or "tryptophan" or "methionine" or "FAs" or "cholesterol" or "PGE2" or "adenosine" from 2005 to 2024, primarily within the past 5 years.

metabolism of CAFs to ameliorate an immunosuppressive TME is still at an early stage, the findings are very encouraging in enhancing anti-tumor immunity and curbing tumor growth.

Conclusions and future directions

Adapted metabolic profiles in tumor cells and CAFs create a TME that contains abundant immunosuppressive metabolites while inadequate essential nutrients, which suppress anti-tumor activities of both intrinsic and adaptive immune cells, ultimately promoting tumor immune evasion. Immunometabolic strategies targeting the critical metabolic pathways in tumor cells have been demonstrated to ameliorate the immunosuppressive TME and boost immune response. More recently, immune cells and CAFs in the TME serve as new targets for immunometabolic therapy. Nanomedicine can improve biodistribution, biocompatibility and bioavailability of metabolic modulators through stimuli-responsive drug release and targeting specific cell types, thus enhancing the efficiency in metabolic reprogramming and minimizing their systemic toxicity. Eventually, nanomedicine-assisted metabolic interventions can effectively and precisely reverse an immunologically cold milieu to an immunologically hot TME (Fig. 3b).

Nanomedicine-aided metabolic reprogramming of the TME for cancer immunotherapy has made great progress in fundamental studies, but clinical translation of this approach is still challenging. Collaborative efforts should be made into the following directions: (1) Unveiling metabolic crosstalk between various cell types in a heterogenous TME; (2) Improving selective targetability of nanomedicine on different cell types within the TME to promote anti-tumor immunity and reduce systemic toxicity; (3) Effectively reactivating anti-tumor immune response of T cells; (4) Reducing nonspecific clearance of nanomedicine by the reticuloendothelial system; (5) Reducing physical and chemical barriers of ECM for the intra-tumoral infiltration of nanomedicine and immune cells; (6) Developing precise and personalized metabolic reprogramming nanomedicine for different patients and/or tumor subtypes; (7) Developing advanced *in vitro* and *in vivo* models for human tumors.

Outstanding questions

Rewriting metabolism via nanomedicine to ameliorate a suppressive TME represents a fascinating approach for tumor immunotherapy, however, clinical trials of this approach remain scarce. To bridge the gap between fundamental research and preclinical/clinical trials: (1) Nanomaterials as vehicles for a broad spectrum of metabolic regulators should be developed with better targetability and higher delivery efficiency to reduce systemic toxicity of metabolic regulators; (2) Immunometabolic nanomedicine should target not only tumor cells but also immune cells and CAFs; (3) Holistically regulating the TME via nanomedicine should be considered, rather than targeting a single cell type, because of the presence of complex metabolic interplay among tumor cells, immune cells and CAFs in the TME, which could effectively potentiate immunometabolic therapy.

Contributors

Jieyu Liu, Xiaoling Li and Kui Luo conceived the outline of this review. Jieyu Liu and Yinan Bai drafted the manuscript and performed the creation of figures, tables and text boxes. Xiaoling Li and Yinggang Li critically revised the review. Kui Luo finalized this manuscript. Jieyu Liu and Yinan Bai contributed equally to this draft. All authors have read and approved the final version of the manuscript.

Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105301.

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