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REVIEW

Nanomedicine-driven tumor glucose metabolic reprogramming for enhanced cancer immunotherapy



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Abstract Tumors exhibit abnormal glucose metabolism, consuming excessive glucose and excreting lactate, which constructs a tumor microenvironment that facilitates cancer progression and disrupts immunotherapeutic efficacy. Currently, tumor glucose metabolic dysregulation to reshape the immunosuppressive microenvironment and enhance immunotherapy efficacy is emerging as an innovative therapeutic strategy. However, glucose metabolism modulators lack specificity and still face significant challenges in overcoming tumor delivery barriers, microenvironmental complexity, and metabolic heterogeneity, resulting in poor clinical benefit. Nanomedicines, with their ability to selectively target tumors or immune cells, respond to the tumor microenvironment, co-deliver multiple drugs, and facilitate combinatorial therapies, hold significant promise for enhancing immunotherapy through tumor glucose metabolic reprogramming. This review explores the complex interactions between tumor glucose

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metabolism—specifically metabolite transport, glycolysis processes, and lactate—and the immune microenvironment. We summarize how nanomedicine-mediated reprogramming of tumor glucose metabolism can enhance immunotherapy efficacy and outline the prospects and challenges in this field.

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1. Introduction

Tumor immunotherapy is a treatment strategy that reactivates, sustains, or enhances the tumor immune cycle, leveraging the body's own immune system to control and eliminate tumors while establishing immune memory^{1,2}. Currently, immunotherapies represented by immune checkpoint inhibitors (ICIs) have demonstrated efficacy across various cancer types^{3–5}. However, the immune evasion mechanisms of tumors—particularly the suppression of effective immune surveillance through alterations in their glucose metabolism pathways—significantly limit the response rates of these therapies⁶. Unlike normal cells, typical tumor cells preferentially generate energy through glycolysis even under oxygen-rich conditions, a phenomenon known as the Warburg effect^{7,8}. During this process, tumor cells increase the transport levels of metabolites, particularly glucose and lactate, upregulate key enzymes involved in the glycolytic pathway, and export lactate as a metabolic byproduct^{9–11}. This not only supports the heightened metabolic demands of tumor progression but also creates a hypoxic and nutrient-deficient tumor microenvironment that limits the proliferation and activation of anti-tumor immune cells. Additionally, the accumulation of lactate further exacerbates the tumor immunosuppressive microenvironment (ITME)^{12,13}. Recently, targeting metabolite transport, key glycolytic enzymes, and metabolite lactate to reprogram tumor glucose metabolism, thereby mitigating the ITME is emerging as a novel strategy in tumor immunotherapy.

Although targeting tumor glucose metabolism holds theoretical promise for “starving” tumor and enhancing immunotherapy efficacy, the clinical application of glucose metabolism modulators (GMMs) still faces numerous challenges. On one hand, certain GMMs, such as nucleic acid-based, small-molecule and protein-based drugs, often exhibit inherent limitations, including poor stability, low solubility, and short half-life, which restrict their bioavailability^{14–16}. Moreover, GMMs are hindered by systemic toxicity and insufficient targeting specificity. For example, glycolytic inhibitors like 2-deoxy-D-glucose (2-DG) have been shown to suppress cancer cell proliferation but simultaneously disrupt T cell glucose metabolism, leading to adverse effects that outweigh potential benefits^{17,18}. The complexity of the TME further complicates the delivery and efficacy of GMMs¹⁹. Tumor cells located near or far from blood vessels rely on different primary metabolic pathways, maintaining cell survival through a sophisticated metabolic symbiosis²⁰. This spatial metabolic heterogeneity enables immune components within the tumor to adapt in a spatiotemporal manner to varying oxygen tensions, glucose availability, and levels of acidification, thereby facilitating the establishment of ITME^{21,22}. Crucially, tumors can activate compensatory metabolic mechanisms to adapt to glucose metabolism inhibition, deriving energy and substrates from alternative pathways, such as fatty acid metabolism, which also adversely affects the immune microenvironment^{23,24}. These characteristics

endow tumors with a degree of drug resistance, posing significant challenges to the use of GMMs for blocking tumor energy supply and reshaping the immune microenvironment.

In recent years, nanomedicines have demonstrated tremendous potential in the field of tumor immunotherapy^{25–28}. Specifically, glucose metabolism modulating nanomedicines (GMMNs) can enhance the stability of GMMs, extend *in vivo* circulation time, and improve their bioavailability^{29,30}. Additionally, leveraging the size-dependent effects of nanomedicines, drug distribution can be optimized to achieve higher tumor-specific drug concentrations, thereby improving the efficacy of metabolic interventions^{31,32}. Through precise compositional design, nanomedicines can be endowed with active targeting capabilities and tumor microenvironment responsive properties, maximizing therapeutic efficacy while minimizing toxicity to healthy tissues^{33,34}. Moreover, through superior assembly or load capabilities, nanomedicines are able to achieve multi-drug co-delivery, effectively targeting tumor metabolic heterogeneity and metabolic compensation, which is also conducive to the combination multiple therapies³⁵. As a result, nanomedicines hold significant promise for correcting abnormal glucose metabolism in tumor cells, reprogramming the ITME, and ultimately enhancing the efficacy of immunotherapy.

This review focuses on the unique roles of tumor glucose metabolism in tumor progression and immune recognition, providing a comprehensive summary of the intricate interplay between glucose metabolism processes—metabolite transport, glycolysis, and lactate—and the tumor immune microenvironment. It explores how the distinctive advantages of GMMNs can be harnessed to effectively drive glucose metabolic reprogramming to enhance immunotherapy, offering novel strategies to overcome tumor resistance to immune-based treatments (Fig. 1). Furthermore, the challenges of GMMNs are also discussed.

2. Interplay between glucose metabolism and immunity

Tumor cells adapt to and exploit their microenvironment through an enhanced aerobic glycolytic process known as the Warburg effect⁷. This glucose metabolic reprogramming not only supports rapid growth and survival but also modulates the immune system response through various mechanisms. In this section, we will explore tumor glucose metabolism and its complex interactions with immune surveillance, focusing on three key aspects: metabolite transport, glycolysis, and lactate.

2.1. Metabolite transport

Metabolite transport plays a crucial role in dysregulated glucose metabolism. To sustain rapid growth, proliferation, and metastasis, tumor cells express a significant number of glucose transporter proteins³⁶. GLUT1 (Glucose Transporter 1), a critical carrier for transmembrane glucose transport, is expressed at low levels in

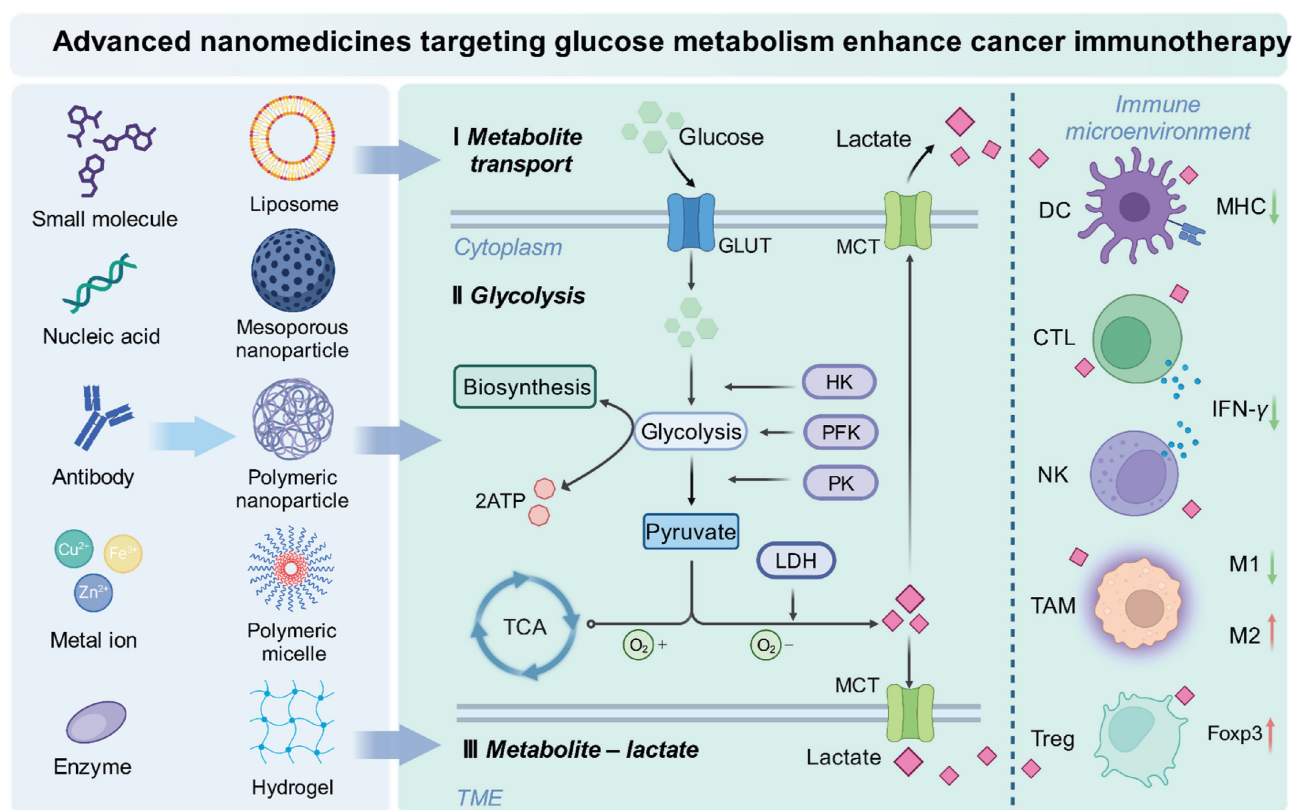


Figure 1 Schematic illustration of nanomedicines modulating tumor glucose metabolism to enhance immunotherapy. I Tumor cells regulate the transport of glucose and the metabolic byproduct lactate through membrane-bound transporters. II Within the cytoplasm, glucose undergoes glycolysis, catalyzed by enzymes such as hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK), producing pyruvate, which is subsequently converted into lactate by lactate dehydrogenase (LDH). III Lactate is then expelled *via* monocarboxylate transporters (MCT), contributing to the acidification of the TME and impacting the proliferation and function of various immune cells, such as dendritic cells (DCs), cytotoxic T lymphocytes (CTLs), natural killer cells (NKs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs). Glucose metabolism modulating nanomedicines (GMMNs) can deliver various types of drugs, regulate tumor glucose metabolism by targeting metabolite transport, glycolysis, and lactate, alleviate the immunosuppressive microenvironment, and improve the effectiveness of immunotherapy.

mammalian embryonic and mature tissues³⁷. However, its expression is markedly increased in hypoxic and ischemic malignant tumor cells and is correlated with tumor progression and patient prognosis^{38,39}. Notably, immune cells, particularly effector T cells and natural killer (NK) cells, require substantial amounts of glucose upon activation to meet their energy and biosynthetic needs, enabling them to exert cytotoxic effects^{37,40,41}. When tumor cells efficiently uptake glucose *via* GLUT1, they create a local energy-deficient environment that intensifies metabolic competition with immune cells, adversely affecting the proliferation and function of effector immune cells. Additionally, this insufficient energy supply may lead to functional polarization of immune cells, promoting the differentiation of T cells into Tregs and the polarization of macrophages of M2 phenotypes, cell types that rely less on glycolysis and are better adapted to low-glucose and high-lactate environments^{42–44}. Wu et al.⁴⁵ discovered that inhibiting GLUT1 increased tumor oxidative phosphorylation (OXPHOS) levels, resulting in excess reactive oxygen species (ROS) production, promoting TNF α -mediated cell death, and enhancing cytotoxic T lymphocyte (CTL) activity against tumor cells (Fig. 2). It is important to note that CD8⁺ T cells predominantly rely on glycolysis for their activation and proliferation, with the rapid glucose transport activity of GLUT1 playing a crucial role in this metabolic process⁴⁶. Notably, GLUT2,

characterized by its lower affinity but higher transport capacity, can also effectively modulate glucose levels within CD8⁺ T cells when glucose concentrations are elevated⁴⁷. This capability enables CD8⁺ T cells to sustain their metabolic activity even when GLUT1 function is compromised, indicating that GLUT1 may represent a highly selective therapeutic target. Overall, GLUT affects the immune microenvironment in a multifaceted manner and thus could be a promising target to alleviate the immunosuppressive microenvironment by precisely modulating glucose transport.

Enhanced glycolytic activity produces substantial amounts of lactic acid, pyruvic acid, and other acidic substances, resulting in lower intracellular pH value⁴⁸. The accumulation of excessive acidic products leads to the acidification of the cellular environment, inhibiting cell growth and potentially causing tumor cell apoptosis⁴⁹. To maintain pH homeostasis, tumor cells excrete lactate *via* monocarboxylate transporter proteins (*e.g.*, MCT1/4) to avoid glycolysis inhibition from negative feedback mechanisms^{48,50}. Upregulation of MCT1/4 has been observed in various malignant tumors, including breast cancer, melanoma, and lung cancer⁵¹. These transporters not only facilitate lactate efflux, supporting efficient glycolysis in tumors and maintaining metabolic symbiosis in metabolically heterogeneous tumors, but also are closely linked to tumor progression, metastasis, and

recurrence^{10,52}. Fang et al.⁵³ have elucidated that MCT4 is markedly overexpressed in HCC. Furthermore, they revealed that MCT4 inhibition can potentiate the expression of the CD8⁺ T cell-recruiting chemokines CXCL9 and CXCL10 via the ROS/NF- κ B signaling pathway, thereby amplifying the antitumor immune response (Fig. 2). For immune cells, Hiroyoshi et al.⁵⁴ revealed that MCT1 plays a crucial role in mediating Treg function under high lactate conditions and is associated with PD-1 expression on Treg. Zou et al.⁵⁵ indicate that MCT1 upregulation mediates the pre-mRNA splicing of Treg *CTLA-4*, promoting the expression of *CTLA-4* and *Foxp3*, which facilitates immune escape.

In summary, tumor cells efficiently utilize transporter proteins such as GLUTs and MCTs to regulate intracellular and extracellular metabolite concentrations. The elevated expression of these transporters not only promotes tumor cell proliferation and survival, but also detrimentally impacts the immune microenvironment. Therefore, targeting key transporters such as GLUT1 or MCT1/4 shows potential in alleviating the immunosuppressive microenvironment and restoring effector immune cell function. However, it is important to note that activated effector T cells, similar to tumor cells, maintain high proliferation rates through aerobic glycolysis and keep glycolytic intermediates at high levels to promote efficient intracellular metabolic synthesis⁵⁶. Consequently, therapies blocking these common glycolytic pathways might inadvertently diminish the immune response. For instance, MCT1 is overexpressed in activated lymphocytes, and its mediated lactate export is crucial for maintaining efficient glycolysis and clonal expansion of activated T cells; disruption of MCT1 activity can lead to reduced lymphocyte proliferation⁵⁷. When the glycolysis of T cells is blocked, their ability to produce IFN- γ is inhibited, leading to a significant reduction in anti-tumor efficacy¹⁰. M1-type macrophages likewise upregulate MCT4 in an NF- κ B-dependent manner, thereby sustaining their efficient glycolysis and anti-tumor inflammatory responses⁵⁸. However, selectively delivering metabolic modulatory drugs to target cells while circumventing competition from malignant cells remains a challenge. Strategies to address these issues could focus on integrating nanotechnology to design more selective and specific therapies that target metabolic pathways in tumor cells while minimizing interference with normal immune cell function.

2.2. Glycolysis

Aerobic glycolysis provides energy for tumor progression. Glucose is metabolized by glycolysis, undergoing multiple reaction steps that culminate in the production of pyruvate. In typical cells with normal blood oxygen levels, most of the pyruvate enters the mitochondria and undergoes oxidative phosphorylation via the tricarboxylic acid (TCA) cycle to produce ATP, meeting the cell's energy requirements^{36,59}. However, in cancer cells, most of the pyruvate produced by glycolysis is converted to lactate by lactate dehydrogenase (LDH/LDHA), bypassing the mitochondria³⁶. Since the energy yield of glycolysis is much lower than that of oxidative phosphorylation, tumor cells enhance metabolic efficiency by increasing the expression and activity of key glycolytic enzymes⁶⁰.

HK, the first key rate-limiting enzyme in the glycolytic pathway, primarily resides on the outer mitochondrial membrane and phosphorylates glucose to glucose-6-phosphate⁶¹. Current studies indicate that the aberrant upregulation of glycolysis in tumor cells promotes the dissociation of HK2 (a subtype of hexokinase) from the mitochondrial membrane, enabling its interaction with cytoplasmic I κ B α . More critically, HK2 not only plays its traditional role in glycolysis but also acts as a protein kinase that phosphorylates I κ B α , leading to NF- κ B-dependent activation of PD-L1 expression, thereby facilitating tumor immune evasion (Fig. 3)⁶². Additionally, Zhang et al.⁶³ revealed that HKDC1, a newly discovered HK isoform, promotes tumor immune escape by activating STAT1/PD-L1 in a CD8⁺ T-cell-dependent manner. Current research indicates that normal tissues predominantly express HK1, while tumor tissues express both HK1 and HK2⁶⁴, suggesting that HK2 could be a potential target to precisely inhibit tumor glycolysis and alleviate the immunosuppressive microenvironment.

PFK is the second rate-limiting enzyme in the glycolytic pathway. There are two types of PFK, PFK1 and PFK2, both of which utilize fructose-6-phosphate and ATP, converting them to ADP and either fructose-1,6-bisphosphate (F1,6BP) or fructose-2,6-bisphosphate (F2,6BP), respectively⁶⁵. High expression and increased activity of PFK not only affect glucose metabolism in tumor cells but also exacerbate the metabolic

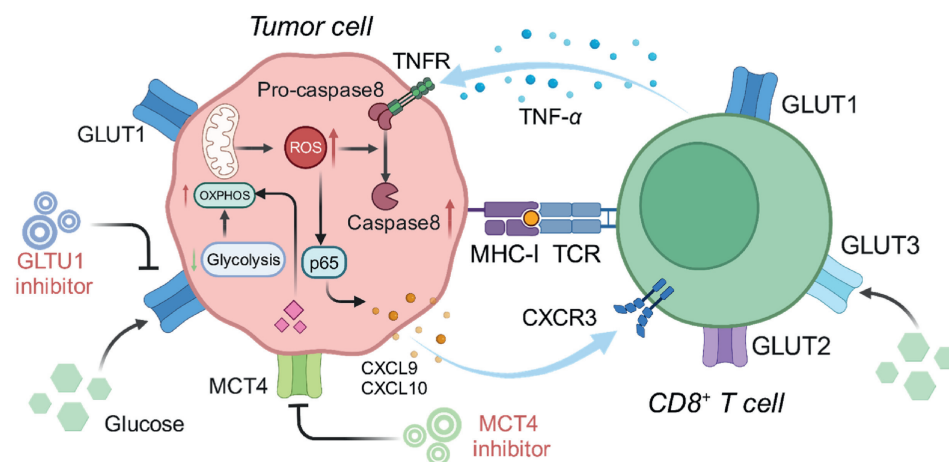


Figure 2 The schematic illustrates that inhibition of GLUT1 results in an increase in the tumor OXPHOS pathway, leading to excessive production of ROS, which subsequently promotes TNF α -mediated cell death. Additionally, the inhibition of MCT4 alleviates the acidic TME and enhances T cell infiltration and immune attack by increasing the expression of CXCL9/CXCL10 through the ROS/NF- κ B signaling pathway.

competition between tumor cells and immune cells, including NK and T cells. This metabolic competition induces acidification of the local microenvironment, indirectly inhibiting anti-tumor immunity⁶⁶. Lee et al.⁶⁷ found that PFKP (isoform of PFK1) activates PI3K in tumor cells, promoting tumor cell progression. Additionally, activation of the PI3K pathway inhibits the differentiation and infiltration of CD8⁺ T cells, promotes the production of Tregs, and polarizes macrophages toward the M2 phenotype, thereby inducing an immunosuppressive microenvironment^{68,69}. However, a direct link between PFK1 and the immune microenvironment has yet to be established.

PK, the third rate-limiting enzyme in glycolysis, catalyzes the irreversible phosphorylation of phosphoenolpyruvate (PEP) and ADP to produce pyruvate and ATP⁷⁰. PKM2 as an isozyme of PK, is widely overexpressed in tumor tissues, predominantly existing in two forms: a tetramer with high enzymatic efficiency, which facilitates the classical glycolytic catalytic function, and a dimer with low enzymatic efficiency, which acts as a transcriptional activator promoting the expression of oncogenes⁷¹. Xia et al.⁷² demonstrated that in pancreatic ductal adenocarcinoma cells, PKM2 shifts from a tetramer to a dimer, simultaneously promoting STAT1 phosphorylation under the action of TGF- β 1. The phosphorylated STAT1 then binds to the PKM2 dimer and translocates to the nucleus, where it enhances PD-L1 expression (Fig. 3). Furthermore, Palsson et al.⁷³ also discovered that treatment with a PKM2 activator (TEPP-46), which induces PKM2 tetramerization, can reduce PD-L1 expression and diminish tumor immune evasion. Current studies have demonstrated that PKM2 can be released into the extracellular environment to mediate intercellular communication through direct secretion or exosomes. Microvesicle-derived PKM2 from hepatocellular carcinoma cells

induces metabolic reprogramming in monocytes and promotes STAT3 phosphorylation in the nucleus, leading to monocyte differentiation into M2 macrophages and the remodeling of the tumor microenvironment⁷⁴. These findings suggest that when targeting PKM, it is essential to deeply understand the distinct roles that different forms of PKM2 play in tumors, and to maintain a degree of flexibility in therapeutic strategies to optimize both metabolic and immune regulation.

In summary, targeting key enzymes of glycolysis is expected to effectively inhibit tumor progression and restore immune surveillance. However, current therapeutic strategies targeting key glycolytic enzymes often focus on the effects of downstream lactate production on the immune microenvironment following glycolytic inhibition, while neglecting the exploration of how these key enzymes influence tumor immunity. Similarly, the potential impact of metabolic substrate changes following metabolic interventions on tumor growth and the immune microenvironment has not been thoroughly investigated. Future research should delve into the direct interactions between key enzymes, metabolic substrates, and tumor immune responses, taking into account the metabolic adaptation mechanisms of tumors and the dynamic changes of relevant enzymes and substrates. This comprehensive understanding could provide novel insights for immune therapies based on glucose metabolism modulation.

Additionally, it is crucial to consider that glycolysis is a fundamental metabolic process in cells, non-specific treatments may disproportionately harm normal cells. In macrophages, inhibition of HK1-dependent glycolysis suppresses LPS- and ATP-induced IL-1 β precursor maturation and caspase-1 activation, and attenuates their antitumor immune effects⁷⁵. As with many targeted therapeutic strategies, prolonged use of inhibitors targeting

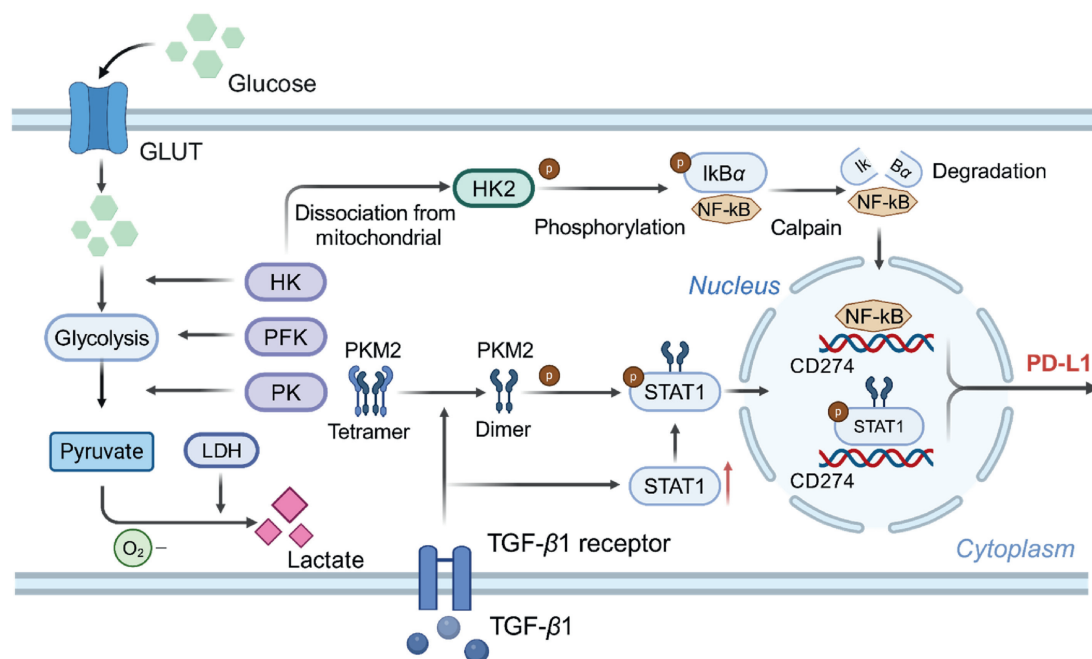


Figure 3 The schematic illustrates the key glycolytic enzyme HK2, under the influence of aberrant tumor glycolysis, phosphorylates I κ B α , promoting NF- κ B nuclear translocation and upregulating PD-L1 expression in tumor cells. Additionally, under the action of TGF- β 1, PKM2 shifts from a tetramer to a dimer, which concurrently enhances STAT1 phosphorylation. The phosphorylated STAT1 then binds to the PKM2 dimer and translocates to the nucleus, further promoting PD-L1 expression. The abnormal upregulation of these key enzymes is strongly correlated with tumor immune evasion, indicating their potential as targets for modulating the immune microenvironment.

glycolytic enzymes may result in tumor cells adapting their metabolic pathways, leading to drug resistance⁷⁶. Tumor cells may activate alternative energy-producing pathways, such as glutamine metabolism or fatty acid metabolism to circumvent treatment. Zhang et al.⁷⁷ found that in the absence or inhibition of PKM2, TNBC cells shifted from glycolysis to mitochondrial respiration, relying on fatty acid β -oxidation for energy. In glioblastoma (GBM), fatty acid oxidation (FAO) has been shown to promote the expression of CD47 through the acetylation of NF- κ B/RelA, thereby facilitating tumor malignancy⁷⁸. Additionally, Andrés et al.⁷⁹ demonstrated that the simultaneous inhibition of HK2 and glutaminase can significantly impact tumor energy metabolism, ultimately delaying tumor formation. Inhibition of over-activated metabolic pathways is feasible, but compensatory effects between multiple metabolic pathways severely limit actual clinical efficacy. Therefore, developing composite therapeutic strategies that can target multiple metabolic pathways simultaneously while incorporating nanotechnology to improve drug targeting ability is promising.

2.3. Metabolite—lactate

Pyruvate is reduced to lactate in the cytoplasm by LDH. Elevated serum levels of total LDH have been observed in patients with breast, pancreatic, and gastric cancers, accompanied by the up-regulation of the LDH-A gene⁸⁰. This is associated with the activation of the vascular endothelial growth factor (VEGF) signaling pathway due to hypoxic stimulation and involvement in tumor neovascularization^{81,82}. Li et al.⁸³ found that LDHA subunits were highly correlated with PI3K activity. However, it is noteworthy that LDHA regulates IFN- γ expression in Th1 cells by modulating the acetylation of histone H3. LDHA deficiency in CD8⁺ T cells decreases their anti-tumor activity, preventing migration and proliferation⁸⁴. Therefore, the issue of targeting LDHA as a potential therapeutic target needs to be considered critically.

2.3.1. Tumor cell

Lactate is produced not only by glycolysis but is also transported into cells through its specific receptor, G protein-coupled receptor 81 (GPR81), or by MCTs⁸⁵. As a product of the glycolytic process, lactate is not merely a waste product of energy metabolism but also a crucial regulator of the TME. By lowering the pH of the TME, lactate directly influences the behavior of tumor cells and their surrounding cells⁴⁹. This acidified environment aids tumor cells in evading immune surveillance and promotes resistance to various chemotherapeutic agents^{52,54,55}. Studies have demonstrated that signaling pathways activated under low pH conditions, such as NF- κ B pathway⁸⁶, enhance the survival of tumor cells and support their continued proliferation and metastasis. Additionally, lactate impacts the expression of cell cycle proteins, driving cell cycle progression and accelerating tumor cell division and proliferation⁸⁷. A novel epigenetic modification—histone lysine lactylation (Kla)—has been confirmed to exist. Lactate-mediated metabolic gene expression induces glucose uptake in tumor cells through changes in histone Kla^{85,88}. In head and neck squamous cell carcinoma (HNSCC), the H3K9la modification has also been shown to activate immune checkpoint genes *via* IL-11, leading to CD8⁺ T cell dysfunction and inducing immune evasion⁸⁹. In summary, for tumor cells, lactate in the TME promotes tumor progression multidimensionally.

2.3.2. CD8⁺ T cell

Lactate not only supports tumor growth but also promotes immune escape by modulating immune cell function in the TME (Fig. 4). As early as 2007, studies showed that increasing lactate concentration in the TME impedes lactate efflux from T cells, thus interfering with their cytotoxic activity⁹⁰. Nowadays multiple potential mechanisms by which lactate affects T cell function have been identified. Lactic acid-induced acidic microenvironment inhibits the expression of nuclear factor of activated T-cells (NFAT) in CD8⁺ T-cells, which impairs IFN- γ production and leads to tumor immune tolerance⁹¹. In addition, lactate accumulation in the microenvironment also interferes with T cell function by inhibiting p38 and JNK/c-Jun signaling⁹². However, within the tumor immune microenvironment, the effects of lactate on cancer cells and immune cells are highly complex and difficult to decipher, a complexity that is further compounded by the acidic protons. Some scholars believe that the impairment of CD8⁺ T cell immune function is primarily due to the highly acidic environment caused by lactate protons, while lactate itself can serve as a metabolic energy source for T cells, thereby contributing to the enhancement of cell viability to some extent⁹³. Lactate has been shown to act as a “fuel” to increase the stemness profile of CD8⁺ T cells, thereby enhancing their anti-tumor immune function⁹⁴. Lactate-pretreated CD8⁺ T cells not only effectively inhibited tumor growth in murine models but also exhibited enhanced T cell clonal expansion *in vivo*⁹⁴. Lactate exerts a complex dual role in T cells. The lactic acid-induced acidic microenvironment can inhibit immune responses, whereas lactate can enhance the antitumor efficacy of CD8⁺ T cells under specific conditions. Thus, targeting the neutralization of the acidic microenvironment, rather than the elimination of lactate itself, provides a novel perspective and direction for advancing tumor immunotherapy and metabolic regulation strategies.

2.3.3. Tregs

Tregs facilitate tumor immune evasion primarily by secreting immunosuppressive cytokines such as TGF- β and IL-10, which directly inhibit the activation and function of effector T cells, NK cells, and dendritic cells, thereby suppressing the overall anti-tumor immune response⁹⁵. In low-glucose environments, Tregs are capable of efficiently utilizing lactate to sustain their immunosuppressive functions and proliferative activity⁹⁶. Lactate has been shown to regulate Tregs activity by mediating MOESIN lactylation and enhancing TGF- β signaling, which aids in Treg maturation and differentiation⁹⁷. Additionally, lactate significantly influences the expression of immune checkpoints on Tregs. It facilitates the splicing of CTLA-4 RNA, thereby promoting CTLA-4 expression in Tregs, which is crucial for maintaining their immunosuppressive function⁵⁵. Tregs have also been found to actively absorb lactate through MCT1, promoting NFAT1 translocation to the nucleus, which in turn enhances PD-1 expression⁵⁴. Overall, lactate plays a positive regulatory role in reinforcing the immunosuppressive functions of Tregs and promotes tumor immune escape (Fig. 4).

2.3.4. DC

DCs are antigen-presenting cells that play a crucial role in initiating and regulating immune responses⁹⁸. Studies have shown that lactate can impair the immune activation of DCs by inhibiting their differentiation and maturation. In a high lactate concentration environment, the antigen-presenting ability and pro-inflammatory

cytokine secretion (Type I Interferon) of DCs are significantly reduced^{99,100}. This occurs because lactate directly interferes with the antigen-presenting function of DCs by inhibiting the NF- κ B signaling pathway and reducing the expression of MHC-II molecules. Additionally, lactate inhibits the function of DCs and diminishes their activation of T cells through the GPR81¹⁰¹. The lactate-induced acidic environment also reduces chemokine secretion by DCs, hindering their migration to lymph nodes and consequently decreasing initial T cell activation (Fig. 4). Hanks et al.¹⁰² found that lactic acid induces DCs to adopt immune-tolerant phenotypes, transforming into regulatory mature dendritic cells (mregDCs)¹⁰². These mregDCs significantly inhibit T cell-mediated anti-tumor responses, thereby aiding tumors in evading immune surveillance¹⁰³. Therefore, therapeutic approaches that modulate lactate levels could help restore the antigen-presenting ability of DCs, enhance tumor recognition and clearance by the immune system, and provide new strategies for anti-tumor immunotherapy.

2.3.5. NK

NK cells perform their anti-tumor effects through direct cytotoxicity or orchestration of a broader immune response¹⁰⁴. The accelerated glycolysis in cancer cells, driven by factors such as hypoxia and oncogenes, creates an unfavorable environment for NK cell activity¹⁰⁵. This accelerated glycolysis not only leads to lactate accumulation but also reduces the availability of glucose in the TME, thereby inhibiting the cytolytic function of NK cells. Lactate in the

TME inhibits NK cell activity through several mechanisms. It has been shown that the lactic acid-induced acidified environment leads to a significant reduction in NK cell activity and decreases mTOR signaling activity, which is detrimental to the survival of NK cells^{106,107}. NFAT is involved in the transcription of IFN- γ , and lactic acid inhibits the upregulation of NFAT, thereby blocking the production of IFN- γ by NK cells upon stimulation (Fig. 4)¹⁰⁸. In addition, lactic acid has also been found to inhibit NK cells from expressing the activation receptor NKp46, which plays a key role in tumor recognition and killing by NK cells¹⁰⁹. It should be noted that the energy source of NK cells is highly dependent on glucose metabolism. Although “starvation therapy”, which aims to control the glucose source of the tumor, can reduce lactate production, it may severely inhibit the anti-tumor activity of NK cells. Utilizing nanotechnology to precisely regulate lactate levels holds promise for improving the anti-tumor activity of NK cells without compromising their energy metabolism, thus providing a more effective strategy for tumor therapy.

2.3.6. TAM

TAMs are macrophages infiltrating the tumor tissue and are the most abundant immune cells in the tumor microenvironment¹¹⁰. These macrophages can undergo different types of activation in the tumor microenvironment, classified into M1-type and M2-type macrophages. M1-type macrophages have pro-inflammatory and anti-tumor effects, while M2-type macrophages are tumorigenic and inhibit the inflammatory response^{110,111}. Several mechanisms

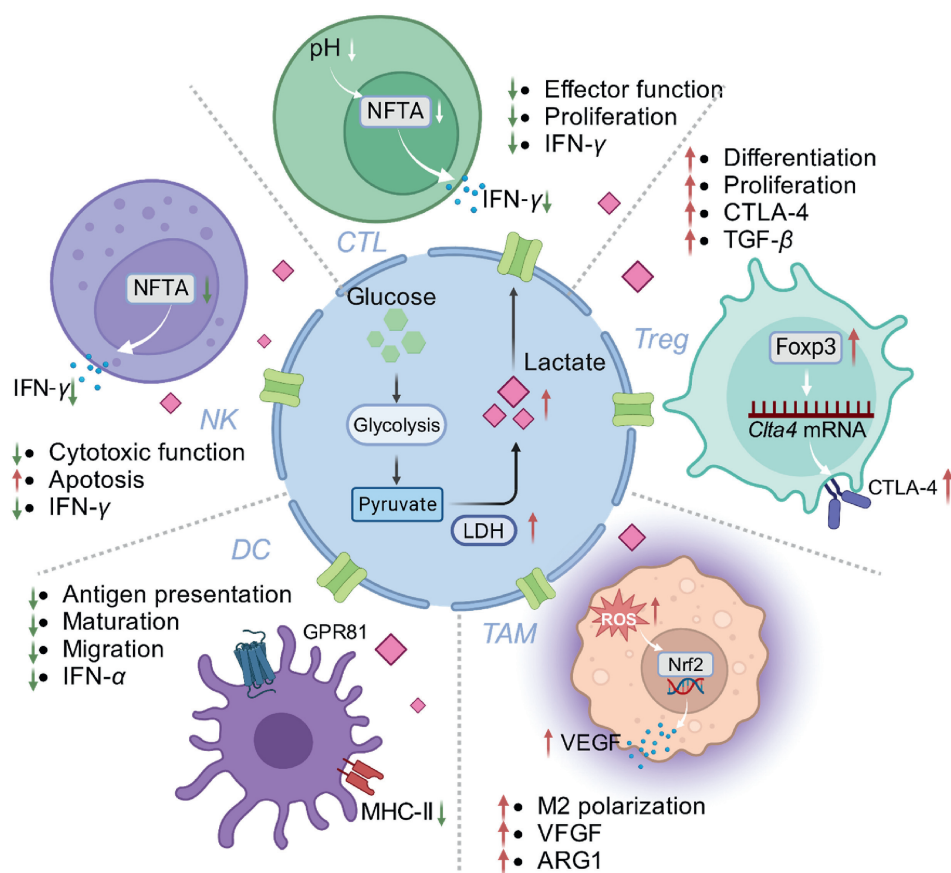


Figure 4 Schematic illustration showing that abnormal tumor glucose metabolism leads to increased lactate levels, acidifying the tumor microenvironment while affecting the proliferation, differentiation and function of immune cells.

by which lactate promotes M2 macrophage polarization have been identified. Lactate can elevate ROS levels in TAMs, which in turn activates the Nrf2 signaling pathway, leading to the induction of M2 macrophage polarization (Fig. 4)¹¹². Additionally, lactate can regulate polarization towards the M2 phenotype by interacting with Gpr132, a G-protein-coupled receptor on the surface of TAMs¹¹³. Chung et al.¹¹⁴ discovered that inhibiting lactate production in tumor tissues with Machilin A in a Lewis lung adenocarcinoma mouse model reduced M2 macrophage polarization and suppressed tumor growth. Notably, M2-TAMs can take up tumor-source lactate *via* MCTs on cell membrane, which leads to the transcription and expression of VEGF and the arginine-metabolizing enzyme arginase-1 (ARG1) genes, promoting neo-vascularization and inhibiting T cell activation and proliferation⁵⁸. The role of lactate in TAMs reflects the highly adaptive nature of the tumor microenvironment. Through metabolic reprogramming, tumor cells generate substantial amounts of lactate, thereby regulating TAMs and creating an environment conducive to their survival and proliferation.

In summary, the role of lactate within the TME is intricate and profound, exerting significant influence on the functionality of both tumor and various immune cells, while exhibiting a degree of duality. By precisely modulating lactate production downstream of glycolysis in tumor cells, it is possible to enhance the antitumor activity of NK and T cells without compromising their energy metabolism. This approach may also reduce the differentiation of immunosuppressive cells such as Tregs, M2 macrophages, and mregDCs. Concurrently, such strategies could aid in restoring the antigen-presenting capabilities of DCs, thereby augmenting antitumor immune responses. However, it is crucial to recognize the dual nature of lactate's role in the TME. The dysfunction of CD8⁺ T cells might be attributed to the acidic environment induced by lactate rather than lactate itself. Conversely, under certain conditions, lactate can enhance the stemness of CD8⁺ T cells, thereby improving their antitumor efficacy; additionally, D-lactate (DL) can induce the polarization of M2 macrophages towards an M1 phenotype^{115,116}. These findings offer critical insights into strategies for remodeling the immune microenvironment through lactate regulation.

3. Nanomedicines modulate abnormal glucose metabolism in tumors

Targeting the three pivotal aspects of tumor glucose metabolism—metabolite transport, glycolysis, and lactate production—offers a compelling and effective strategy for reshaping the immunosuppressive microenvironment. However, current GMMs such as small molecules, enzymes, nucleic acid drugs, antibodies, and metal ions face challenges related to stability, targeting precision, and specificity, often resulting in unexpected toxicities and limited efficacy. The advent of nanomedicines holds promise for significantly improving the delivery of free drug molecules *in vivo*, thereby enhancing therapeutic benefits. In this context, we will review the latest advancements in employing GMMNS to target these metabolic pathways, achieving tumor glucose metabolism reprogramming and providing new insights for enhancing cancer immunotherapy through metabolic intervention (Table 1).

3.1. Nanomedicines modulate metabolite transport

As previously mentioned, metabolite transport plays a crucial role in sustaining the high-throughput glucose metabolism of tumors

and in creating an immunosuppressive microenvironment. Compared to free glucose metabolism modulators, using nanomedicines to regulate tumor metabolite transport has demonstrated significant advantages in several preclinical models (Table 1). For instance, Zhang et al.¹¹⁷ developed a carrier-free nanomedicine by using the GLUT1 inhibitor Genistein, which not only avoids the toxicity associated with carriers but also effectively enhances cellular uptake of Genistein. By inhibiting glucose transport, achieving a starvation treatment for Lewis lung cancer. In another study, Wang et al.¹¹⁸ ingeniously combined the use of BAY-876-loaded nanomedicines to inhibit GLUT1 with the tumor-targeting properties of EcN bacteria, which actively home to tumor sites and competitively consume glucose through bacterial respiration, synergistically suppressing tumor glucose metabolism. Using glucose oxidase (GOx) to catalyze the conversion of β -D-glucose into gluconic acid and hydrogen peroxide (H_2O_2), thereby inhibiting glucose supply, holds promise for fundamentally suppressing tumor glucose metabolism. Building on this concept, Li et al.¹⁶ synthesized a functional glycopolymer (GP) featuring a caged dual donor of H_2S and H_2O_2 and used it to encapsulate GOx. This GP is responsive to the reductive conditions of the tumor microenvironment, enabling the on-demand release of GOx, which effectively disrupts the metabolic plasticity and adaptability of tumor cells. Moreover, to address the potential off-target effects of systemic GOx administration, Xiao et al.¹¹⁹ proposed an injectable *in situ* hydrogel system (GPI/R848@ALG) for the localized delivery of GOx. This approach precisely cuts off the energy supply necessary for tumor growth and metabolism, thereby enhancing the applicability of GOx in cancer treatment.

Tumor cells regulate lactate uptake and efflux through the activity of monocarboxylate transporters, specifically MCT1 and MCT4, to establish metabolic symbiosis among tumor cells and mediate immune evasion. Targeting these MCTs therefore offers a promising strategy for cancer therapy. Han et al.¹²⁰ developed a nanomedicine (NP2) loaded with the MCT1/4 inhibitor syrosingopine (Syr), which is designed to release Syro in response to ROS in the tumor microenvironment. This approach effectively prevents lactate efflux, leading to a rapid accumulation of intracellular lactate and demonstrating excellent therapeutic efficacy in osteosarcoma model. Similarly, Wu et al.¹²¹ reported a hollow Fe_3O_4 nanozyme carrier co-loaded with lactate oxidase (LOX) and Syro (Syr/LOD@HFN), which releases Syro and LOX in response to the acidic tumor microenvironment, achieving synergistic treatment of B16-F10 melanoma. Furthermore, Wang et al.¹²² designed a pH-responsive nanomedicine (PBNM) targeting MCT4 with siRNA, effectively reversing the intracellular and extracellular pH gradient and inhibiting stemness and lung metastasis of Huh-7 hepatocellular carcinoma.

3.2. Nanomedicine regulates glycolysis process

Tumor cells accelerate glucose metabolism by regulating key enzymes in the process of glycolysis, which provides targets for metabolic regulation in tumors⁴⁵. Tumor cells significantly upregulate PKM2, redirecting glucose metabolism from the normal respiratory chain to the tumor-specific aerobic glycolysis pathway. Zhang et al.¹⁵ designed a glioblastoma-targeting nanocapsules with siRNA targeting PKM2 at its core, encapsulated by a methacrylate-TMZ shell, which is formed through *in situ* polymerization with a GSH-responsive crosslinker. The nanocapsules, modified with ApoE peptides on its shell, efficiently crosses the

Table 1 List of GMMNs targeting metabolite transport, glycolysis and lactate.

Mechanism	GMMN	Cargo	Principle	Advantage	Cancer model	Ref.
Metabolite transport	GC NPs EcN@HPB	Genistein BAY-876; EcN	GLUT1 inhibition GLUT1 inhibition; glucose limitation	Carrier-free nanomedicine Combined bacterial targeting	Lewis lung cancer CT26 colorectal cancer	117 118
	GP GPI/R848@ALG NP2 Syr/LOD@HFN	Gox Gox Syrisingopine Syrisingopine LOX	Glucose limitation Glucose limitation MCT1/4 inhibition MCT1/4 inhibition; Lactate removal	Reduction-responsive release Injectable hydrogel delivery ROS-responsive release pH-responsive release	4T1 breast cancer 4T1 breast cancer K7M2 osteosarcoma B16-F10 melanoma	16 119 120 121
Glycolysis	PBNM APOE-MT/siPKM2 LSN	siMCT4 siPKM2 Lonidamine	MCT4 silence PKM2 silence HK2 inhibition	pH-responsive release Permeate the BBB GSH-responsive release	Hepatocellular carcinoma GL261 glioblastoma 4T1 breast cancer	122 15 123
	CL HPP-Ca@GSK VNP _{siLdha} LND@HMPB-Zn	Lonidamine GSK2837808A siLdha Zn ²⁺	HK2 inhibition LDHA inhibition LDHA silence LDHA inhibition; LDHA efflux	Active targeting properties Active targeting properties Optimizing pharmacokinetics NIR-responsive release	4T1 breast cancer 4T1 breast cancer B16-F10 melanoma B16 melanoma	124 125 126 127
Metabolite-lactate	ODMSN-AQ4N-LOX PLNP ^{Cu}	LOX LOX; Cu ²⁺	Lactate removal Lactate removal Radical generation	Efficient drug delivery Multi-drug co-delivery	4T1 breast cancer 4T1 breast cancer	128 129
	LDO	CoMnFe	Lactate removal	High enzyme reaction rate	Uveal melanoma	130

BBB via LDLR-mediated endocytosis, precisely targeting GBM and facilitating PKM2 degradation. Similarly, HK2 is another critical enzyme in the glycolytic process. Liu et al.¹²³ developed a GSH-responsive nanomedicine that co-delivers LND and NLG919 to simultaneously inhibit HK2 in tumor cells and disrupt the immunosuppressive microenvironment, effectively suppressing the growth of 4T1 tumors. By blocking glycolysis, LND reduces ATP levels, limiting the energy supply to tumor cells and creating a favorable environment for apoptosome assembly. Building on this concept, Han et al.¹²⁴ designed a biomimetic lipid nanomedicine co-loaded with LND and cytochrome C (Cyt C) and combined with a tumor-homing peptide, LinTT1, to enhance targeting efficiency. This approach enables precise regulation of glycolysis, leading to the effective inhibition of breast cancer progression¹²⁴. Currently, research on inhibitors targeting the PFK site remains limited, and no reports have emerged on developing nanomedicines based on PFK inhibitors to reverse tumor progression. However, with further advancements in PFK inhibitor research, new targets for correcting tumor glucose metabolism are expected to emerge.

3.3. Nanomedicines target metabolite-lactate

Lactate, as a direct product of the glycolytic process, accompanies abnormal glucose metabolism and increases production levels, and is a key regulator of the TME as well as a key target for nanomedicines. LDHA is typically overexpressed in glycolytic cells and catalyzes the conversion of pyruvate to lactate, making it a promising target for inhibiting lactate production at its source. Yan et al.¹²⁵ proposed a metal-phenolic nanomedicine (HPP-Ca@GSK) modified with hyaluronic acid (HA) to deliver GSK2837808A, effectively eliminating tumor LDHA and creating a high-glucose, low-lactate microenvironment, thereby enhancing breast cancer treatment efficacy. Targeted silencing of LDHA via siRNA is another viable approach. However, it's important to note that siRNA, as a nucleic acid-based therapeutic, is prone to rapid degradation and clearance in systemic circulation. To address this, Zhang et al.¹²⁶ developed a cationic lipid-assisted nanoparticle (VNPsiLdha) based on FDA-approved polymers for systemic siRNA delivery. This system effectively prevents premature siLdha release *in vivo* and improves its accumulation in tumors, thereby reducing LDHA expression. Additionally, excessive intracellular zinc ions have been shown to decrease LDHA activity or enhance its efflux. Building on this, Meng et al.¹²⁷ constructed an intelligent LND@HMPB-Zn nanosystem for the co-delivery of LND and Zn²⁺, effectively achieving dual inhibition of glycolysis.

LOX catalyzes the oxidation of lactate to pyruvate and hydrogen peroxide, making it a useful tool for lactate clearance in the TME. However, since lactate concentrations in the TME can vary between 10 and 40 mmol/L¹²⁸, sufficient LOX concentrations and controlled LOX release are necessary for safe and effective lactate removal. In response, Tang et al.¹²⁹ designed novel openwork@dendritic mesoporous silica nanoparticles (ODMSN), whose porous structure provides ample physical space for LOX loading, achieving high drug loading capacity and sustained release. This approach led to a 99.9% reduction in lactate concentration within the TME, thereby inhibiting tumor progression. In addition, Kang et al.¹³⁰, while using LOX to degrade lactic acid, made full use of the catalytic product H₂O₂. Though the advantages of nanomedicines, they co-loaded Fenton reagent (such as Cu²⁺) to catalyze hydrogen peroxide to produce more

cytotoxic hydroxyl radicals (OH), forming a “lactic acid processing factory” and achieving 88% tumor inhibition. Nanozymes, a type of nanomaterial with biocatalytic function, have the characteristics of efficient catalysis¹³¹. They can not only mimic the structure of natural enzymes, but also have the effect of nanoparticles. Based on this, Jia et al.¹³² constructed a new type of double-layer nanozyme with extremely high lactic acid catalysis efficiency, which can achieve efficient lactic acid removal in uveal melanoma, enhance ROS production and oxygen production, and achieve the remodeling of the TME.

In summary, GMMNs have demonstrated certain advantages over free drugs in regulating tumor metabolite transport, glycolysis pathways and metabolite lactate. However, existing GMMNs therapeutic strategies still face some challenges due to the lack of in-depth understanding of the characteristics of tumor glucose metabolism and its relationship with the immune microenvironment. For example, the metabolic heterogeneity of tumors not only mediates the metabolic symbiosis of tumors to promote tumor progression, but also confers certain drug resistance to tumors. Moreover, the metabolic compensation problem of tumors also makes it impossible to completely block the energy supply of tumors by inhibiting a single metabolic pathway. At the same time, the possible off-target effects of some nanomedicines due to insufficient targeting, the toxic side effects caused by non-specific enrichment of drugs are all obstacles to the use of GMMNs to regulate tumor glucose metabolism and enhance the immunotherapeutic effects.

4. Advanced nanomedicine modulating glucose metabolism strategy to enhance immunotherapy

To effectively enhance immunotherapy through the intervention of tumor glucose metabolism with nanomedicines, it is crucial to gain a deep understanding of the tumor's unique metabolic characteristics and their relationship with the immune microenvironment, while maximizing the inherent advantages of GMMNs. These advantages primarily include targeting ability, responsive release, multi-drug co-delivery and combination therapy. The targeting specificity of advanced GMMNs ensures selective action on tumor cells without compromising the function of normal immune cells, thereby augmenting the benefits of immunotherapy¹³³. Furthermore, the modifiable nature of nanomedicines allows for their design to achieve responsive release within the tumor-specific lactate microenvironment, thereby minimizing off-target toxicities^{134–137}. The multifunctionality of nanomedicines enable them to concurrently target multiple metabolic pathways, effectively addressing the metabolic compensation mechanisms of tumors and thereby enhancing the efficacy of antitumor immunotherapy^{138,139}. Finally, nanomedicines can form the basis for combinations with therapies beyond immunotherapy, enabling a multilayered treatment strategy and improving overall efficacy (Table 2). This section will focus on the unique metabolic characteristics of tumors and the metabolic microenvironment they create, summarizing and analyzing how nanomedicines can precisely modify tumor metabolism and optimize immunotherapy through their advantages (Fig. 5).

4.1. Nanomedicines achieve precise targeting

Improving drug targeting to precisely act on target cells is crucial for achieving precise tumor treatment. Nanomedicines can achieve passive targeting to tumor sites due to their size, shape

characteristics, and the inherent enhanced permeability and retention (EPR) effect¹⁴⁰. While this approach allows for localized drug accumulation to some extent, the lack of specificity may not effectively address the metabolic heterogeneity of tumors, potentially leading to unexpected side effects. For example, as noted, both activated effector T cells and tumor cells rely on aerobic glycolysis to maintain high proliferation rates and efficient intracellular metabolism⁵⁶. The absence of active targeting in metabolic pathway regulation may simultaneously compromise the immune response. GMMNs can be equipped with active targeting capabilities through additional modifications based on antigen–antibody interactions, ligand–receptor binding, or aptamer targeting, thereby enhancing their precision and effectiveness¹⁴¹. For example, Li et al.¹⁴² developed a pH-responsive nanomedicine (SK-NPs) that encapsulates a glycolysis inhibitor along with the PD-L1 siRNA, and is modified with folate acid (FA) to achieve FA receptor-specific recognition. This nanomedicine demonstrated excellent targeting capability for folate receptor-positive cells, thereby minimizing the impact on effector T cells (Fig. 6). Additionally, a sophisticated targeting strategy was developed by Hu et al.¹⁴³ They engineered nanoparticles (AbCholB) comprising phenylboronic acid-modified cholesterol and albumin, which form cholesterol-glucoside-like structures within cancer cells. This structure induces lysosomal damage and inhibits mTOR function, thereby selectively inhibiting the metabolic activity of cancer cells, while sparing normal cells from severe damage due to their competitive disadvantage in nutrient uptake.

Targeting tumor-infiltrating immune cells and precisely modulating their metabolic processes represent promising strategies for cancer therapy. Unlike pro-inflammatory M1 macrophages, which primarily rely on aerobic glycolysis for their tumor-suppressive functions, pro-tumor M2 macrophages depend mainly on oxidative phosphorylation for their energy supply^{43,58}. Therefore, precisely increasing the glycolysis level in TAMs and promoting the polarization of M1-type macrophages can enhance the anti-tumor immune response. To achieve this, Guo et al.¹⁴⁴ employed CD206, a receptor highly expressed on TAMs, as a target by modifying DSPE-PEG-mannose on nanomedicine (siRNA@M-PTX-CA-OMVs) loaded with the siRNA targeting glucose metabolism regulator Redd1, enabling precise metabolic regulation of TAMs (CD206-mannose), which enhances the level of intracellular glycolysis and promotes the polarization of M1-type macrophages (Fig. 6). Additionally, given that DL may polarize M2 TAMs towards M1 TAMs, Han et al.¹¹⁶ developed nanomedicine (DL@NP-M-M2pep) delivering DL specifically to M2 macrophages, effectively alleviating the immunosuppressive microenvironment in HCC. This approach further enhanced its anti-tumor effect when combined with an anti-CD47 antibody (Fig. 6). Through targeted modification by nanotechnology, such precise regulatory strategies avoid competition from malignant cells and efficiently inhibit tumor progression. In conclusion, the intelligent design of GMMNs must consider not only the targeting ability but also the metabolic properties of immune cells and tumor cells, to achieve precise and efficient tumor therapy.

4.2. Nanomedicines achieve responsive release

Non-specific, broad-spectrum modulation of systemic glucose metabolism can lead to severe metabolic disorder syndromes^{145,146}. The TME is characterized by unique features such as hypoxia, acidity, elevated levels of lactate, ROS, matrix

Table 2 List of GMMNs that facilitate precise targeting, responsive drug release, co-delivery of multiple drugs and synergistic therapeutic strategies.

Strategy	Category	GMMN	Cargo	Mechanism	Ref.
Precise targeting	Tumor cell targeting	SK-NPs	SK; siPDL1	Inhibits glycolysis; blocks immune escape	140
	Infiltrating immune cells targeting	AbCholB	Boric acid group; cholesterol	Passive targeting through nutrient competition	141
Responsive release	pH response	siRNA@M-/PTX-CA-OMVs	siRedd1	Regulation of TAM glycolysis	142
	GSH response	DL@NP-M-M2pep	D-lactate	Promotion of M1 TAM polarization	116
Multidrug co-delivery	ROS response	Gd/CeO ₂	Syr; LOX	Inhibiting lactate production; promoting lactate degradation	143
	Small molecule and nucleic acid co-delivery	LSN	Lon	Inhibits HK2 and blocks glycolysis	123
	Metal ion and peptide co-delivery	PD-G@BC	BPTES; CPI-613	Blocks glucose metabolism; inhibits glutamine metabolism	144
	Metal ion and enzyme co-delivery	MONs@LND/PAH-cit//PEI@siGLS	Lon; siGLS	Simultaneous inhibition of glycolysis and glutamine synthesis	145
		Zn-Car	Zn ²⁺ ; carnosine	Simultaneous inhibition of glycolysis and OXPHOS	146
Combined therapies	Chemotherapy	YHZ	LOX; Zn ²⁺	Disruption of tumor metabolic symbiosis	147
	Photodynamic therapy	DHCRJ NPs	DOX; IQ1	Improvement of immunogenicity and chemosensitivity	148
		MnZ@Au	Carbon dots; Au	Enhancement of PDT effects by alleviating anaerobic and high glucose metabolism	149
	Photothermal therapy	CM-ZIF8@Ce6/Lon	Ce6; Lon	Improvement of immunogenicity and PDT effect	150
		APG NRs	Polydopamine; GOX	Inhibiting energy supply and HSP70 expression	151
Radiotherapy		RPP/pHCP	Polydopamine; resveratrol	Improvement of immunogenicity and PTT sensitivity	152
		PCCE@fCaCO ₃ -PEG	Fe ³⁺ ; perfluorosebacic acid	Reversal of hypoxia and radiotherapy resistance	153

metalloproteinase-2 (MMP-2), and GSH. These distinctive properties provide essential guidelines for the design of smart, responsive therapeutics^{50,147,148}. Nanotechnology enables the design of smart GMMNs that release drugs in response to specific tumor microenvironmental stimuli, thereby enhancing therapeutic effects and reducing damage to normal cells. Zhao et al.¹⁴⁹ constructed a novel pH-responsive MOF nanomedicine with a core-shell structure (Gd/CeO₂), encapsulating the small molecule drug Syrosingopine (Syr) to inhibit lactate transport and efflux. Concurrently, LOX was chelated on the surface of this nanomaterial to reduce intracellular lactate by catalyzing its degradation within the cell. This acidic environment-driven nanomedicine can target focal tissues through peripheral blood, remodeling the immune microenvironment by breaking down lactate at the focal site through the dual action of Syr and LOX (Fig. 7).

The TME typically exhibits high oxidative stress and generates high levels of ROS, partly due to the high metabolic rate and abnormal angiogenesis required for rapid tumor cell proliferation¹⁵⁰. Exploiting the high ROS characteristics of tumor cells, Yu et al.¹⁵¹ designed a thioketal (TK)-containing GEM precursor self-assembled to construct lactate-responsive nanomedicine (PD-G@BC)co-loaded with the glutaminase inhibitor BPTES and the pyruvate dehydrogenase complex inhibitor CPI-613 to synergistically block glucose and glutamine metabolism in tumor cells (Fig. 7). In conclusion, precisely engineered GMMNs with responsive properties to the tumor microenvironment offer significant advantages in reducing nonspecific accumulation and enhancing bioavailability.

4.3. Nanomedicines achieve multidrug co-delivery

Tumor cells, due to their rapid proliferation and high metabolic demands, tend to obtain energy and necessary survival substances through multiple metabolic pathways¹⁵². When one metabolic pathway is blocked, tumor cells can quickly activate other metabolic pathways to bridge the energy gap, limiting the effectiveness of single-target therapy. For instance, when the glycolytic pathway is inhibited, tumors enhance fatty acid β -oxidation, which fuels mitochondrial oxidative phosphorylation and thus promotes malignant progression⁷⁷. Considering the flexibility of tumor metabolic patterns is crucial for designing effective cancer treatment strategies.

GMMNs integrate multiple drugs into a single nanocarrier through mechanisms such as covalent bonding, physical adsorption, hydrophilic and hydrophobic interactions, and layer-by-layer self-assembly. This enables simultaneous targeting of different metabolic pathways, effectively blocking the metabolic compensation mechanisms of tumor cells. For instance, Zhang et al.¹⁵³ utilized the porous nature of mesoporous silica to simultaneously encapsulate the glycolysis inhibitor LND alongside anti-glutaminase siRNA results in the inhibition of glycolysis, thereby reducing lactic acid production, while concurrently down-regulating glutaminase expression to diminish glutamine uptake by tumor. This dual action remodels metabolic and nutrient partitioning, thereby enhancing nutrient availability for T cells and bolstering anti-tumor immunity (Fig. 8). Additionally, Lei et al.¹⁵⁴ employed metal coordination self-assembly principles to engineer nanomedicines (Zn-Car). These advanced nanocarriers obstruct the copper supply to mitochondrial cytochrome C oxidase in tumor cells, disrupting its activity. Simultaneously, they facilitate the release of copper-responsive drugs, thereby achieving a potent dual inhibition of both oxidative phosphorylation and glycolysis

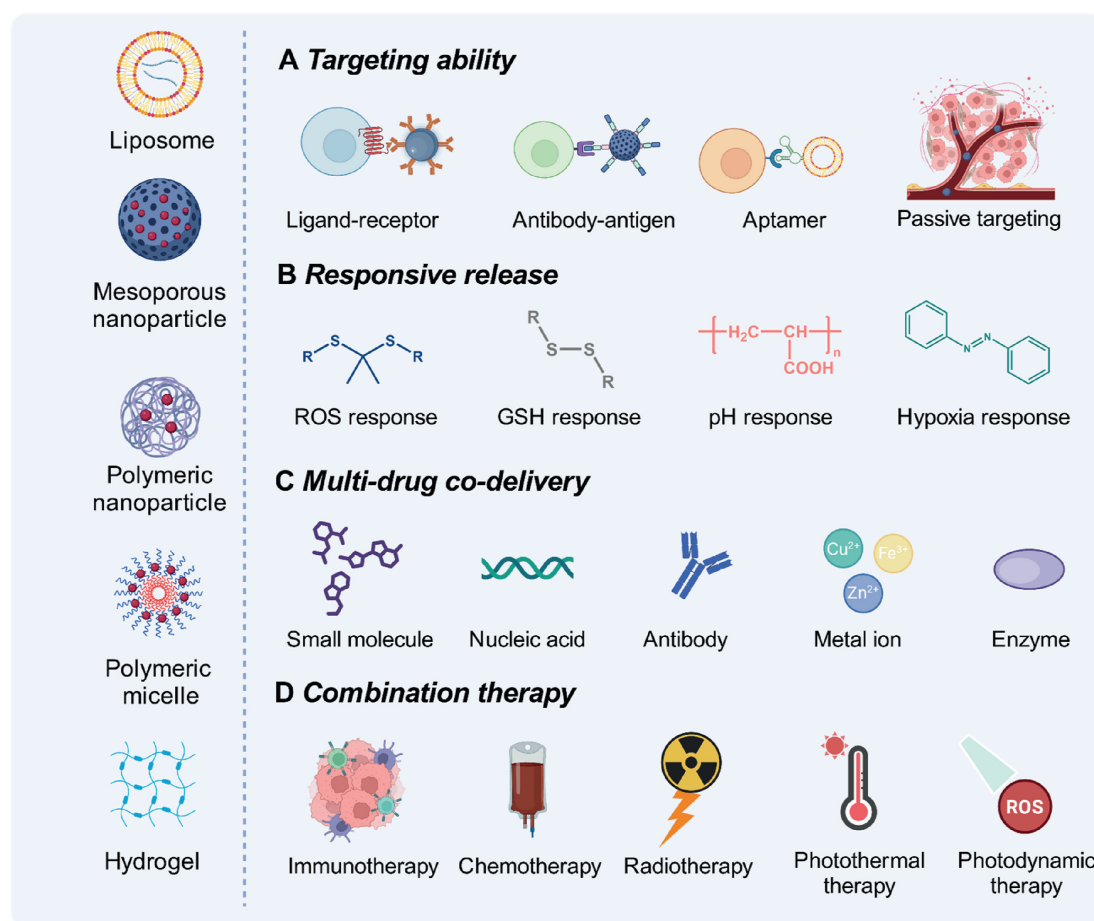


Figure 5 GMMNs facilitate the co-delivery of multiple drugs, responsive drug release, precise targeting, and synergistic therapeutic strategies, thereby modulating tumor glucose metabolism to alleviate the immunosuppressive microenvironment and enhance the efficacy of immunotherapy.

(Fig. 8). Benefiting from the advantages of nanomedicines, such multi-drug co-delivery strategies for regulating multiple metabolic pathways achieve superior therapeutic outcomes compared to the simple combination of two drugs.

The metabolic patterns among different tumor cells exhibit highly heterogeneity¹⁵⁵. Oxygen-rich tumor cells adjacent to blood vessels absorb large quantities of lactate *via* MCT1, utilizing it for energy production in the TCA cycle. Conversely, tumor cells located in hypoxic regions, distant from blood vessels, rely on glucose uptake for glycolysis to generate energy, expelling the produced lactate *via* MCT4 to support oxidative cellular capacity^{156,157}. This metabolic coupling establishes a symbiotic framework, enabling tumor progression within hostile microenvironments and develop unique drug resistance mechanisms²². Immune components undergo adaptive phenotypic alterations driven by spatial variations in the abundance and activity of nutrients or metabolic byproducts. Recent studies highlight significant phenotypic heterogeneity among intratumoral T cells, which may originate from distinct clonal populations with varying proliferative capacities and polarization states^{22,158}. Notably, TAMs and Tregs also exhibit pronounced spatial-functional heterogeneity, profoundly influencing clinical prognosis and therapeutic responses^{159,160}. Beyond immune cells, cancer-associated fibroblasts (CAFs) exhibit metabolic adaptability in response to tumor heterogeneity. Metabolic CAFs (mCAFs), predominantly located in stromal regions, employ Warburg-like metabolism to

supply glycolytic lactate and pyruvate to oxygen-rich tumor cells^{161,162}. Furthermore, their high density drives fibrosis, creating a physical barrier that impairs immune cell infiltration and ultimately contributes to poor clinical outcomes¹⁶³. To overcome the challenges posed by the heterogeneity of tumor glucose metabolism, Qu et al.¹⁶⁴ designed a tumor metabolic symbiosis disruptor to efficiently target the metabolic heterogeneity of tumors. This strategy combines a biocompatible probiotic yeast with a functional enzyme-encapsulated metal-organic framework. The probiotic yeast competitively consumes glucose, reducing its availability to glycolytic tumor cells. Simultaneously, the enzyme-encapsulated framework catabolizes lactic acid, preventing its utilization by oxidizing tumor cells. This dual approach ultimately depletes energy resources, disrupts metabolic symbiosis in the tumor microenvironment, and inhibits tumor progression (Fig. 8).

The multi-drug co-delivery strategy simultaneously targets multiple metabolic pathways, thereby attenuating the metabolic compensation capacity of tumor cells. Additionally, the synergistic effects of the combined drugs possess the potential to address the metabolic heterogeneity of tumors^{154,164}. However, the disparate physicochemical properties of different drugs pose challenges in achieving efficient loading and controlled release within a single nanomedicine. Factors such as drug hydrophilicity, molecular weight, and interactions with the carrier materials can significantly influence the loading efficiency and release kinetics of the drugs within the nanocarrier, which is crucial for the precise

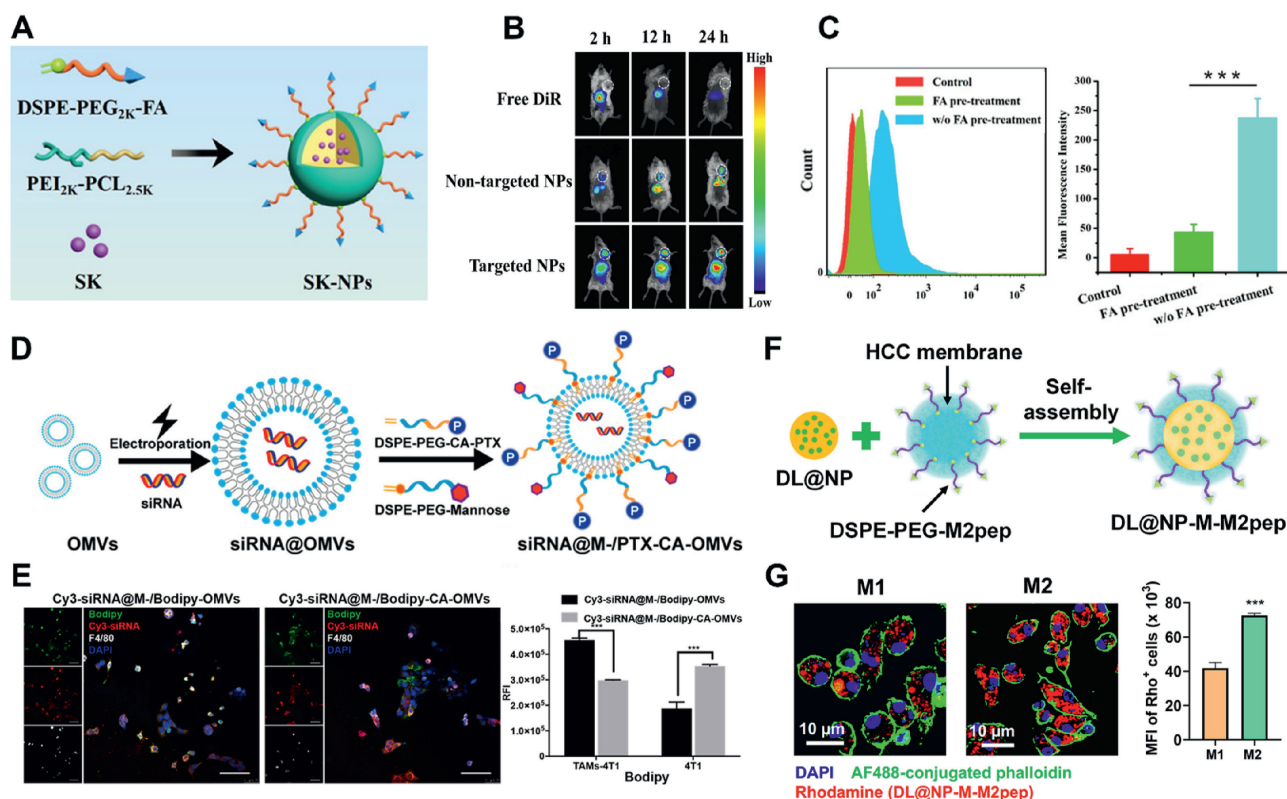


Figure 6 GMMNs achieve precise targeting (A) SK-NPs are surface-modified with DSPE-PEG_{2K}-FA, endowing them with tumor-targeting capabilities, (B) ensuring efficient accumulation at the tumor site, (C) and demonstrating remarkable specificity even when co-incubated with FA pre-treated cells. Reprinted with the permission from Ref. 140. Copyright © 2020 American Chemical Society (D) siRNA@M/PTX-CA-OMVs are modified with DSPE-PEG-mannose, (E) achieving precise targeting of TAMs. Reprinted with the permission from Ref. 142. Copyright © 2021 American Chemical Society (F) DL@NP-M-M2pep is encapsulated within HCC cell membranes modified with macrophage-binding peptide (M2pep), further enhancing the targeting performance of nanomedicines and enabling precise regulation of M2 cells. Reprinted with the permission from Ref. 116. Copyright 2023 American Association for the Advancement of Science.

regulation of tumor glucose metabolism. By employing the precise construction of intelligent GMMNS, it is possible to achieve smart drug release. Moreover, innovations in nanocarrier design, including surface modifications and the development of multi-layered architectures, can significantly enhance drug loading and release profiles. These advancements pave the way for more precise drug delivery strategies, thereby offering promising avenues for the enhancement of anti-tumor therapies.

4.4. Nanomedicines achieve combined therapies

Combined therapeutic strategies are increasingly demonstrating their substantial potential in cancer treatment. By integrating multiple therapeutic modalities, these strategies can enhance treatment efficacy and overcome the limitations associated with monotherapies, such as suboptimal therapeutic outcomes and the rapid emergence of drug resistance. In particular, the therapeutic strategy based on glucose metabolism regulation can realize the regulation of tumor drug resistance, hypoxia, radiotherapy resistance, photothermal resistance and immune microenvironment, providing a solid theoretical basis for the combination of chemotherapy, photodynamic therapy, radiotherapy, photothermal therapy and immunotherapy^{165–169}. However, despite these advantages, the practical application of such combination therapies faces significant challenges. The differing pharmacokinetics and

biodistribution profiles of various therapeutic agents make it difficult to synchronize their proportions and timing of delivery to the tumor site, often resulting in suboptimal clinical outcomes. Nanomedicines offer a promising solution as a drug delivery platform, capable of optimizing the dosing regimens of multiple agents and efficiently integrating dual therapeutic modalities.

The overexpression of HK2, PFK, and PKM2 in various solid tumors, due to metabolic abnormalities^{170–172}, is a significant cause of tumor cell resistance to chemotherapeutic agents such as 5-fluorouracil, epirubicin, and platinum¹⁷³. Targeting tumor glycolysis is therefore anticipated to enhance tumor sensitivity to chemotherapeutic drugs and bolster the body's anti-tumor immune response, creating favorable conditions for the combined application of chemotherapy and immunotherapy. Wang et al.¹⁷⁴ developed dual-activated self-assembled synergistic prodrug nanoparticles (DHCRJ NPs) with antioxidant effects. Leveraging the synergistic action of DOX@HA and JQ1, DHCRJ NPs significantly increased tumor immunogenicity and activated anti-tumor immunity through the antigen-processing and delivery pathway. JQ1, with the assistance of ROS depletion, down-regulates the HK-2 signaling axis, a key regulator of tumor glycolysis, and remodels the lactate-driven ITME (Fig. 9). Remarkably, a synergistic effect was observed, where half the dose of DHCRJ NPs achieved greater efficacy compared to monotherapy.

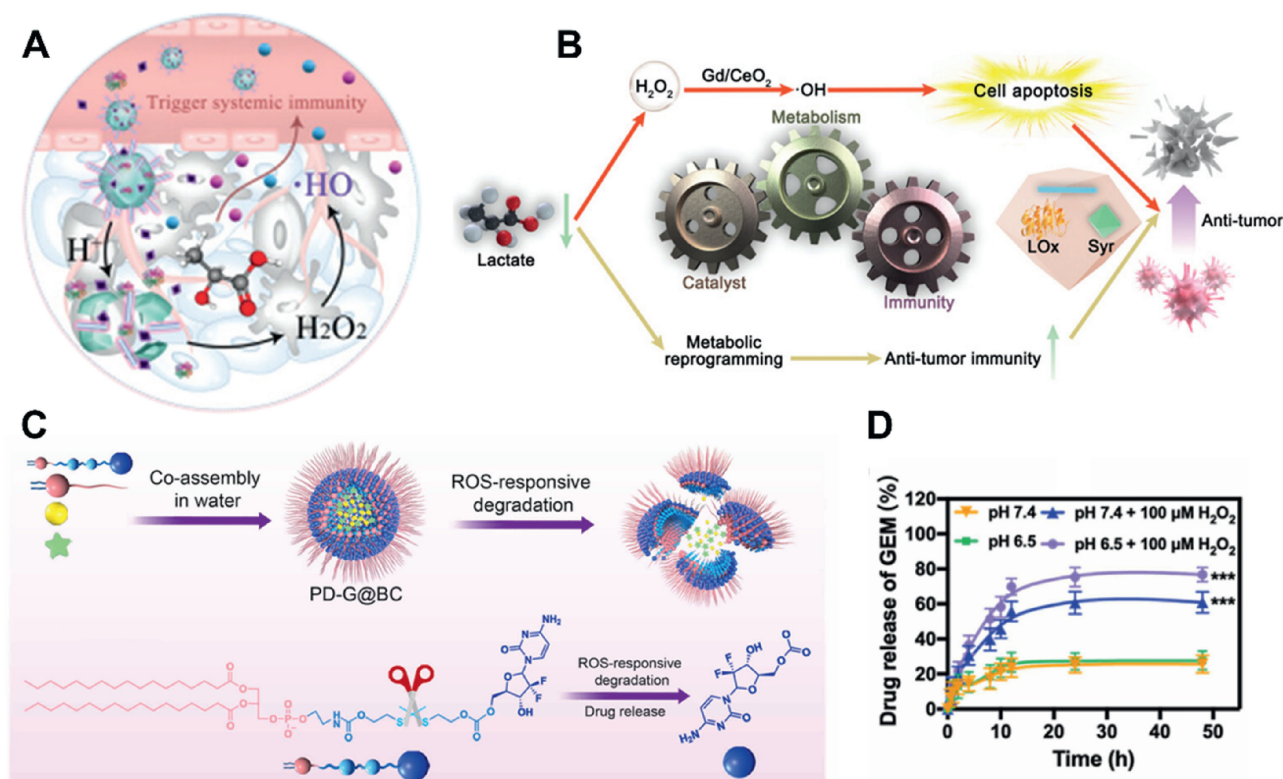


Figure 7 GMMNs respond to tumor microenvironment for precise drug release (A) Schematic illustration showing Gd/CeO₂ releasing LOX and Syr in response to the acidic tumor microenvironment, (B) promoting intratumoral catalytic elimination of lactate to simultaneously enable immune remodeling and catalytic generation of ·OH for tumor therapy. Reprinted with the permission from Ref. 143. Copyright © 2022 Wiley (C) Schematic depicting GEM prodrug self-assembled nanomicelles PD-G@BC, achieving ROS responsiveness via TK (D) Validation of ROS response properties of PD-G@BC in vitro release assays. Reprinted with the permission from Ref. 144 Copyright © 2022 Elsevier.

Photodynamic therapy (PDT) relies on the accumulation of photosensitizers at the tumor site, which generate ROS under irradiation with specific wavelengths of light, inducing apoptosis and necrosis of tumor cells¹⁷⁵. However, the elevated levels of anaerobic glycolysis in tumors result in excessive lactate accumulation, which in turn facilitates the clearance of free radicals and ROS, significantly compromising the clinical efficacy PDT¹⁶⁶. To address these challenges, Nie et al.¹⁷⁶ designed a bifunctional cascade nano-enzymatic catalytic system (MnZ@Au) that regulates the anaerobic microenvironment and glucose metabolism. This system enhances photodynamic efficacy through cascade catalytic reactions, increasing drug penetration and improving anaerobic and glucose metabolism, effectively inhibiting tumor growth. Theoretically, PDT can directly kill tumor cells and induce immunogenic cell death (ICD), releasing immunostimulatory damage-associated molecular patterns (DAMPs), thereby enhancing tumor immunogenicity and revitalizing the patient's intrinsic immune system. Consequently, the combination of PDT and immunotherapy overcomes the limitations of each modality when used alone, synergistically creating a highly immunogenic tumor microenvironment. Modulating glycolysis metabolism further enhances this process by decreasing the antioxidant capacity of tumor cells, boosting therapeutic effectiveness synergistically. Based on this, Luo et al.¹⁷⁷ encapsulated the tumor metabolism modulator Lon and the photosensitizer dihydroporphyrin (Ce6) in ZIF8 metal-organic framework nanoparticles (CM-ZIF8@Ce6/Lon) (Fig. 9). This GMMN releases LDN and Ce6 to inhibit the

abnormal glucose metabolism of tumor cells while inducing the ICD of tumor cells, significantly realizing the photodynamic-immunological synergistic therapeutic effect.

Photothermal therapy (PTT) is a non-invasive and spatially controllable approach to tumor treatment, wherein light energy is converted into heat at the tumor site to induce tumor cell death¹⁷⁸. However, during the PTT process, the damaged tumor cells significantly upregulate glucose metabolism to generate increased energy, thereby inducing the expression of heat shock protein 70 (HSP70), which triggers a cellular thermoprotective response¹⁶⁷. Consequently, inhibiting tumor glucose metabolism and reducing ATP synthesis hold the potential to enhance the response rate of photothermal therapy. In this context, Wu et al.¹⁷⁹ designed a multifunctional nano-reactor, where an Ag-Cu alloy core generates substantial hydroxyl radicals to degrade HSP70, while an outer layer of polydopamine/GOx serves as a photothermal agent and disrupts the ATP energy supply pathway, effectively inhibiting HSP70 expression through this dual strategy. PTT-induced tumor cell damage leads to the release of numerous tumor-associated antigens, effectively activating the body's anti-tumor immune response¹⁸⁰. Therefore, a photothermal-immune synergistic therapy strategy based on glucose metabolism modulation also shows promising potential. Wang et al.¹⁸¹ developed a degradable photothermal nanocarrier (RPP) composed of polydopamine nanoparticles and a cationic polymer, designed to deliver a heat-activated CRISPR/Cas9 plasmid (pHCP) and the natural glucose metabolism modulator resveratrol (Res), thereby enabling PD-L1

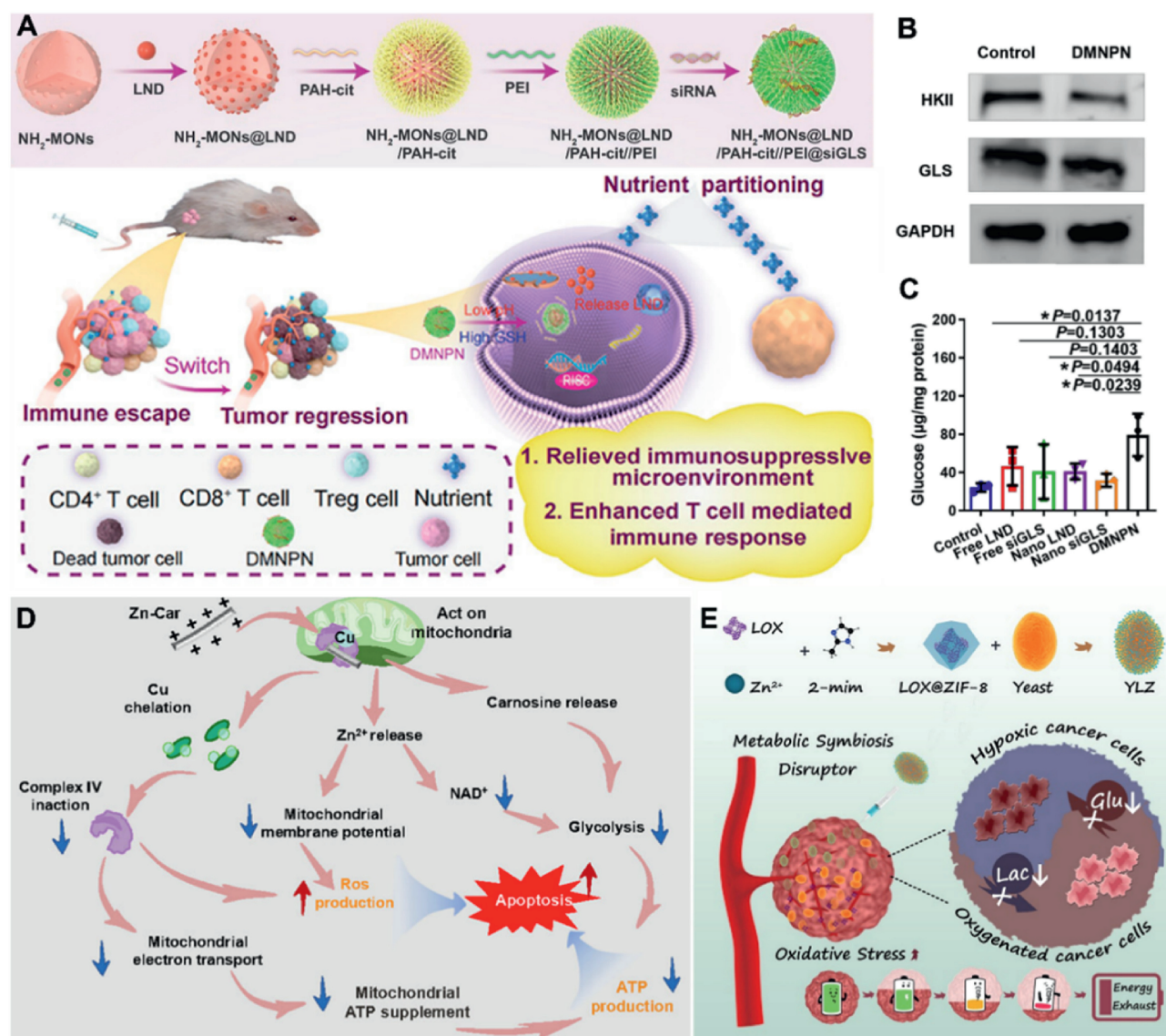


Figure 8 Multi-drug co-delivery by nanomedicines for dual targeting of metabolic pathways and tumor metabolic heterogeneity (A) Schematic illustration showing mesoporous silica simultaneously loaded with Lon and anti-glutaminase siRNA, effectively alleviating the immunosuppressive microenvironment, enhancing T cell-mediated immune response, and demonstrating the nanomedicine's inhibition of tumor (B) glutamine metabolism and (C) glycolysis. Reprinted with the permission from Ref. 145. Copyright © 2023 American Chemical Society. D) Schematic illustration depicting the Zn-Car nanomedicine, constructed via metal coordination self-assembly, targeting both mitochondrial OXPHOS activity and glycolysis, leading to a significant decrease in ATP levels. Reprinted with the permission from Ref. 146. Copyright © 2023 American Chemical Society (E) Schematic illustration of the YLZ bioreactor acting as a tumor metabolic symbiosis disruptor for potent inhibition of metabolically heterogeneous tumors. Reprinted with the permission from Ref. 147. Copyright © 2022 Elsevier.

genomic editing and glucose metabolism regulation in tumor cells, enhancing photothermal efficiency while remodeling the immunosuppressive tumor microenvironment.

The aerobic glycolysis pathway in tumor cells creates a high-lactate and hypoxic tumor microenvironment, reducing local radiosensitivity^{182,183}. Activation of glucose metabolism-related pathways, such as PI3K/AKT, and the expression of hypoxia-inducible factor-1 (HIF-1), also contributes to radiation resistance in tumor cells¹⁶⁸. Intervening in key enzymes of glucose metabolism, key signaling pathways, and HIF-1 has been shown to regulate and reverse glucose metabolism, thereby increasing radiotherapy (RT) sensitivity. Ionizing radiation from RT

promotes the breakage and release of dsDNA in the cell nucleus and increases mitochondrial membrane permeability, leading to mtDNA release. Notably, both DNAs are key mediators in initiating the cGAS–STING pathway. cGAS–STING activation-induced release of type I interferon is essential for DCs¹⁸⁴. Additionally, RT can upregulate MHC-1 molecules, often absent or under-expressed in tumor cells, thereby expanding the pool of antigens available for presentation. Similar to PDT, RT can induce immunogenic cell death, enhancing tumor immunogenicity and promoting immune cell infiltration^{184,185}. Therefore, modulating tumor glucose metabolism can improve the efficacy of both radiotherapy and immunotherapy. Dong et al.¹⁸⁶ developed a

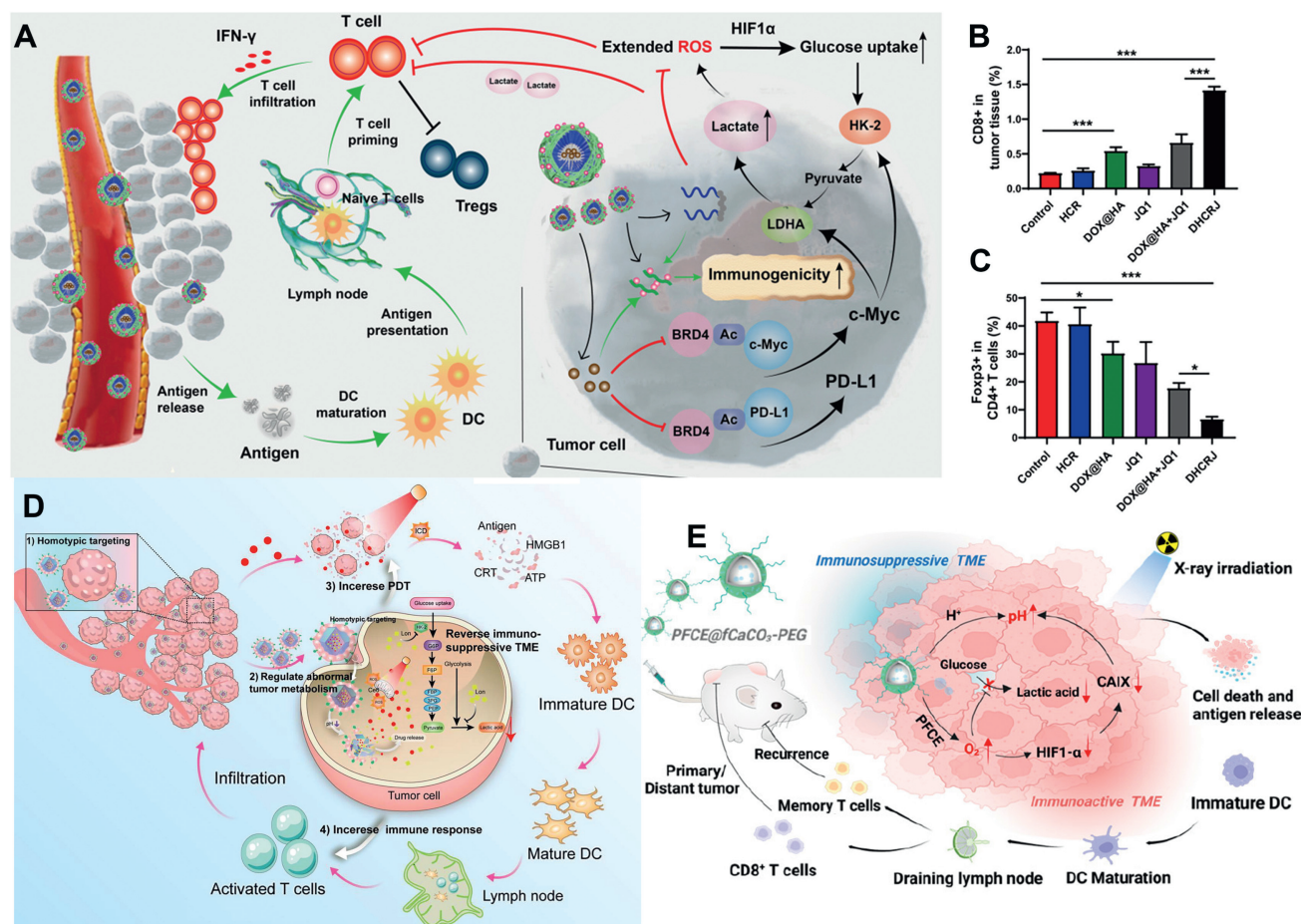


Figure 9 GMMNs achieve dual therapy synergism based on glucose metabolism modulation (A) Schematic illustration showing DHCRJ releasing JQ1 and DOX@HA prodrug in response to elevated intracellular ROS levels. The synergistic action of DOX@HA and JQ1 significantly enhances tumor immunogenicity and activates anti-tumor immunity (B) Flow cytometry analysis revealed an upregulation of tumor-infiltrating CD8⁺ T cells and (C) a downregulation of Treg cells in presence of DHCRJ. Reprinted with the permission from Ref. 148. Copyright © 2022 Elsevier (D) Schematic illustration showing CM-ZIF8@Ce6/Lon utilizing the homotypic targeting properties of the tumor cell membrane to actively target tumor tissues, responsively releasing Ce6 and Lon. Ce6 triggers PDT, inducing ICD and stimulating an anti-tumor immune response. Lon blocks the HK signaling pathway, inhibiting abnormal tumor cell metabolism and remodeling the ITME, thereby enhancing Ce6's photodynamic efficiency and immune response. Reprinted with the permission from Ref. 150. Copyright © 2023 Elsevier (E) Schematic illustration showing PFCE@fCaCO₃-PEG, which features efficient oxygen loading capacity and proton neutralization ability, reducing HIF-1 α expression levels and intracellular lactate production. This effectively reverses radio-resistance induced by hypoxia and acidic micro-environments, ultimately activating anti-tumor immune responses. Reprinted with the permission from Ref. 153. Copyright © 2022 American Chemical Society.

multifunctional fluorinated calcium carbonate nanomodulator (PFCE@fCaCO₃-PEG) (Fig. 9). By limiting lactic acid production and reacting with extracellular protons to neutralize the acidic tumor microenvironment, they reversed radiotherapy resistance induced by tumor hypoxia and acidic. This approach synergistically induced protective anti-tumor immunity, effectively responding to tumor rechallenge.

In summary, enhancing the synergistic effects of immunotherapy with other treatments through metabolic intervention has shown considerable potential. However, the complex metabolic mechanisms by which tumor cells evade immune attack and the specific metabolic needs of immune cells remain not fully understood, limiting the exploration of metabolic regulation in combination with other therapies. Nonetheless, as research into the metabolic regulation mechanisms within the tumor microenvironment deepens, the unique advantages of nanomedicines are

expected to further overcome the limitations of single therapies, particularly in improving therapeutic efficacy, precise targeting, overcoming drug resistance, reducing side effects, and enabling multifunctional applications.

5. Conclusion and prospects

In this review, we summarized how tumors leverage abnormal glucose metabolism-focusing on metabolite transport, glycolytic pathways, and lactate production-to shape a pro-tumor microenvironment that facilitates rapid progression and immune evasion. These findings highlight the therapeutic potential of targeting glucose metabolism in tumor immunotherapy and present a range of promising therapeutic targets. Notably, GMMNs demonstrate notable advantages by improving the stability and circulation time of modulators while enabling

precise tumor targeting, stimuli-responsive drug release, co-delivery of multiple agents, and combination therapies through sophisticated design^{144,149,153,174}. Thus, advanced GMMNs offer significant potential for correcting aberrant tumor glucose metabolism and enhancing the outcomes of cancer immunotherapy.

Although GMMNs are typically designed to target specific metabolic pathways, their carrier materials or excipients, often considered inert components, may exert unexpected metabolic interventions within the tumor microenvironment. For instance, certain nanomaterials can alter local pH, redox states, or ion concentrations, indirectly affecting metabolic pathway activity and even inducing effects opposite to the intended regulation^{187–189}. Commonly used silica materials, have been shown to disrupt glucose and amino acid metabolism in normal hepatocytes¹⁹⁰. Such complex metabolic interferences may compromise the efficacy of targeted regulation and potentially reshape the tumor immune microenvironment—a consideration often overlooked in the current safety and efficacy evaluations of GMMNs. Therefore, future GMMNs development must comprehensively assess the systemic impacts of various components on metabolic and immune pathways, optimizing the composition and synergistic mechanisms of nanomedicines to ensure precision and stability in metabolic regulation.

The metabolic and functional characteristics of tumors and immune cells are highly susceptible to alterations induced by genetic or non-genetic environmental factors during treatment²². This metabolic adaptability and flexibility underscore the necessity of precisely optimizing the timing of drug release in GMMNs. Future designs of GMMNs should incorporate these dynamic changes to ensure that drugs are released at the optimal time when tumor cells are most vulnerable. Real-time monitoring of key metabolites (*e.g.*, lactate, glucose, and pyruvate) in the tumor microenvironment can provide valuable feedback, enabling timely adjustments to the drug release mechanism. Furthermore, the release timing of GMMNs should also consider the metabolic status and functional activity of immune cells. For instance, during the activation phase of cytotoxic immune cells triggered by antigen release following energy blockade, the timely release of immune modulators can further amplify the immune response. Such strategically timed interventions will significantly enhance overall therapeutic efficacy. By integrating these optimizations, GMMNs not only maximize the disruption of tumor metabolism but also effectively modulate the immune microenvironment, thereby boosting anti-tumor immunity.

In-depth exploration of the differences between tumor cells and normal cells in metabolic rates and metabolic pathway selection can provide new opportunities for the development of precise metabolic intervention strategies. For example, CTLs highly express the glucose transporter protein GLUT3, and inhibition of GLUT 1 may have less impact on CTL function, suggesting that we can optimize the therapeutic effect by selectively inhibiting specific targets¹⁹¹. In addition, in tumor treatment, it is also crucial to deeply understand the complex relationship between glucose metabolism and tumor immune microenvironment. In most of the existing strategies that use nanomedicines to regulate glucose metabolism and reshape the immune microenvironment, the impact on immune cells is often superficially evaluated from the perspective of their quantity and function, lacking underlying exploration of their direct impact at the molecular and genetic levels, which will also limit

the actual clinical transformation of nanomedicines. To this end, this article summarizes in detail the complex molecular mechanism between a series of targets in the glucose metabolism and immune cells, aiming to provide more references for the design of nanomedicines and the evaluation of therapeutic effects, and to improve the clinical transformation potential of nanomedicines.

The establishment of a standardized and streamlined GMMNs platforms, tailored to the metabolic and immune characteristics of individual patients, represents a crucial direction for the future of cancer treatment. Currently, strategies utilizing GMMNs, including those related to clinical trials for metabolic therapies, often adopt a “one-size-fits-all” approach, overlooking the metabolic differences among various tumor histological types and between different patients^{119,120,192,193}. The heterogeneity of tumor metabolism is evident not only in the metabolic characteristics of different cells within the same tumor but also in the metabolic responses of patients with the same tumor type. For instance, TNBC can be metabolically classified into lipogenic, glycolytic, and mixed subtypes based on metabolic gene characteristics. Consequently, GMMNs targeting glycolysis may be ineffective against the lipogenic or mixed subtypes of TNBC¹⁹⁴. Therefore, future research should focus on leveraging multi-omics analyses to identify key metabolic targets across different tumors. Additionally, enhancing the dynamic tracking of metabolic changes will be essential for the timely identification of adaptive metabolic alterations in tumors. Ultimately, the development of targeted metabolic intervention strategies, integrated with universal nanoplatforms, will allow for the full utilization of the unique advantages of nanomedicine, thereby achieving efficient precision medicine.

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Conflicts of interest

The authors declare no conflicts of interest.

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