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Review article

Biochemical hallmarks-targeting antineoplastic nanotherapeutics

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ABSTRACT

Tumor microenvironments (TMEs) have received increasing attention in recent years as they play pivotal roles in tumorigenesis, progression, metastases, and resistance to the traditional modalities of cancer therapy like chemotherapy. With the rapid development of nanotechnology, effective antineoplastic nanotherapeutics targeting the aberrant hallmarks of TMEs have been proposed. The appropriate design and fabrication endow nanomedicines with the abilities for active targeting, TMEs-responsiveness, and optimization of physicochemical properties of tumors, thereby overcoming transport barriers and significantly improving antineoplastic therapeutic benefits. This review begins with the origins and characteristics of TMEs and discusses the latest strategies for modulating the TMEs by focusing on the regulation of biochemical microenvironments, such as tumor acidosis, hypoxia, and dysregulated metabolism. Finally, this review summarizes the challenges in the development of smart anti-cancer nanotherapeutics for TME modulation and examines the promising strategies for combination therapies with traditional treatments for further clinical translation.

1. Introduction

Malignant tumors remain one of the leading causes of human death worldwide [1]. Despite significant advancements in optimizing drug delivery systems for solid tumors, the treatment results for cancer patients remain suboptimal due to challenges, including short systemic circulation time, insufficient drug accumulation, inadequate tumor penetration, and intracellular disposition of drugs in the tumor lesions [2,3]. In response, the nanoscale drug delivery systems (nano-DDSs) have been developed to improve the therapeutic modalities from indiscriminate systemic dosing to targeted, highly precise medicines [4–6]. The ultimate aims include extended systemic circulation, enhanced cell uptake, and increased accumulation in the tumors through an enhanced permeability and retention (EPR) effect, also regarded as the passive targeting ability of nanomedicine delivery to the tumors as a result of compromised blood vessels and impaired lymphatic drainage in the tumor tissues. In addition, decorating nanoparticles with various targeting ligands that specifically recognize the tumor tissues or cells through ligand−receptor interactions to further enhance drug delivery effectiveness [7]. Nevertheless, inevitable obstacles, such as the physical and biological barriers within the tumor microenvironments (TMEs), constrain the therapeutic efficacy of nanomedicines [8,9].

The TMEs consist of all constituents surrounding the cancer cells at the location of tumor, such as the extracellular matrices (ECMs), stromal cells (*e.g.*, tumor-associated fibroblasts, mesenchymal stromal cells, pericytes, and adipocytes), immune cells (T and B lymphocytes, natural killer cells, and tumor-associated macrophages), and tumor lymphatic vascular systems [10]. TMEs feature physical aberrancies, including abnormal tumor vasculature, elevated interstitial fluid pressure, increased solid stress, and strengthened ECM stiffness, as well as

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biochemical anomalies, including tumor hypoxia, acidosis, and dysregulated metabolism [11,12]. These pathologic conditions have been reported to have significant impacts on tumorigenesis, heterogeneity, progression, metastases, and resistance to cancer therapies, presenting formidable obstacles to effective drug delivery [10,13]. Therefore, there has been a growing interest in modulating TMEs as a theranostic strategy against malignant tumor cells, especially as an essential strategy to enhance nanomedicines.

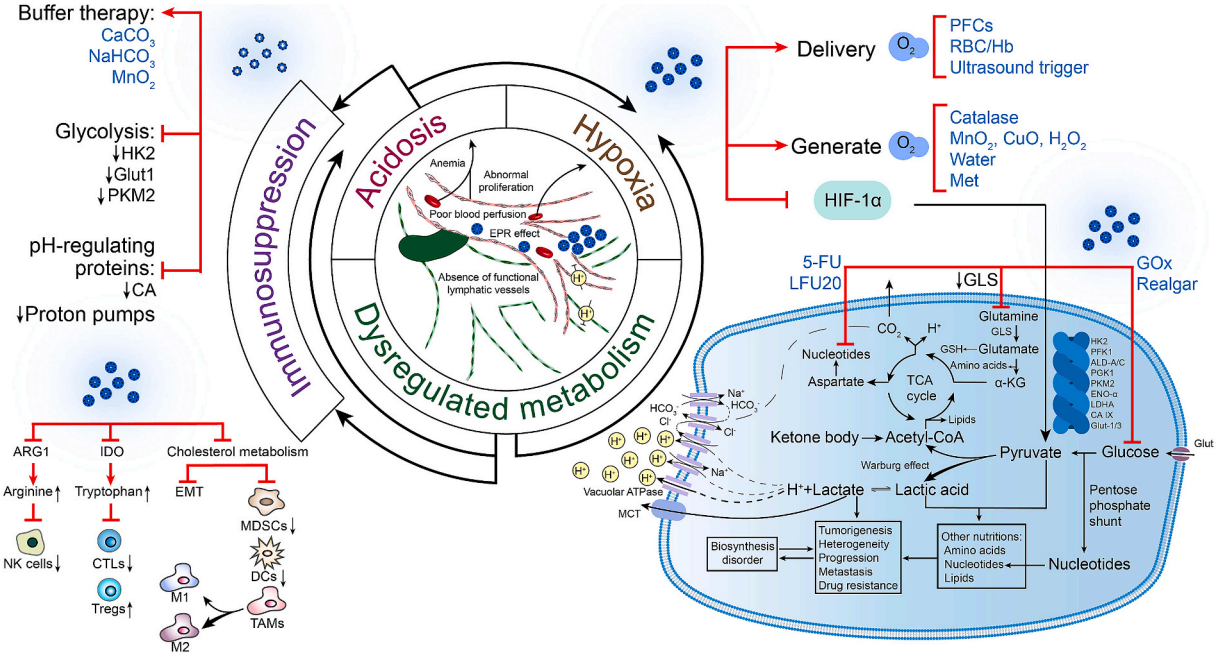
Along with the rapid development of nanotechnology in biomedicine, the unique anti-cancer nanotherapeutics targeting TMEs have recently become a research hotspot. Leveraging the features of TMEs, these nano-DDSs are engineered to be activated under specific conditions to achieve a tailored spatiotemporal modulation of TMEs. For example, numerous stimuli-responsive nanosystems, such as pH-responsive, hypoxia-responsive, ROS-responsive, and even multi-responsive systems, have been extensively utilized in cancer therapy to achieve the goal of sequential drug release and cascade therapy due to their high target specificity, multifunctionality, and superior biocompatibility [14–18]. To date, great progress has been made in developing nanotherapeutics that exploit the abnormal biochemical hallmarks of TMEs.

However, most reviews have focused on the strategies for fabricating stimuli-responsive nanoplatforms that are capable of sensing changes, such as low pH in the TMEs, and triggering rapid drug release in response to specific oncological conditions. To the best of our knowledge, only a few reviews are dedicated to nanotherapeutics that aim to regulate and normalize the biochemical microenvironments. Also, we noticed that tumor acidosis, hypoxia, and dysregulated metabolism have become the hot spot issues in the research on the TMEs. These factors are often interrelated and mutually influence each other, collectively shaping the growth and development of tumors. Understanding and intervening in these interrelationships are of crucial importance for cancer therapy.

Distinguishing itself from the physical microenvironments of tumors, such as abnormal tumor vasculature and elevated interstitial fluid pressure, we focus on the features of biochemical hallmarks, including tumor acidosis, hypoxia, and dysregulated metabolism for an overview and commence with the origins of TMEs, followed by a discussion of the latest strategies in nanotherapeutics to modulate TMEs. Scheme 1 depicts major aspects of nanomedicines for regulating the biochemical hallmarks of TMEs and lists representative drug categories. Additionally, we enumerate the challenges and outline prospective developments of these nanotherapeutics, casting a spotlight on TMEs for enhanced anti-cancer efficacy.

2. Neutralization of tumor acidity

The increased metabolic rate and alterations in metabolic pathways in the tumors often lead to acidosis in the poorly perfused regions [19]. Several sophisticated processes and molecular pathologies contribute to the acidic extracellular tumor pH (pHe) and include the following: 1) In contrast to normal cells, which generate energy primarily by oxidative phosphorylation under aerobic conditions, the cancer cells reprogram metabolic pathways and mostly rely on glycolysis to produce energy, even when there is sufficient oxygen (O_2), which is called the "Warburg effect" [20]. This leads to an elevated conversion of glucose to lactate and H^+ in the tumors. The metabolic intermediates, including lactate and pyruvate, can be utilized for the synthesis of amino acids, nucleotides, and lipids, providing tumors an optimal advantage [21]. The increased lactate is then exported into the extracellular microenvironments through monocarboxylate transporters (MCTs), further decreasing pHe [22]. 2) The abnormal stability of hypoxia-inducible factor-1α (HIF-1α) exacerbates the acidic microenvironments by driving cell metabolism toward the glycolysis pathway [23]. The process involves regulating glycolysis and lactate production genes, such as hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), aldolase-A/C (ALD-A/C), phosphoglycerate kinase 1 (PGK1), enolase-α (ENO-α), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA). 3) To adapt to extensive protons and maintain an appropriate intracellular pH compatible with cell survival and proliferation, the cancer cells launch various compensatory mechanisms, including short- and long-term mechanisms [24]. Short-term mechanisms refer to quick buffering responses, including immediate transfer of acid from the cytosol to organelles, and long-term mechanisms rely on regulating multiple proteins importing weak bases, such as bicarbonate (HCO_3^-), and exporting weak acids, such as carbon dioxide, carbonic acid, and lactate [25]. In addition, hydrions are expelled directly from cells either through transmembrane channels for exchange with Na^+, Cl^-, and other ions, or by



Scheme 1. Nanotherapeutics regulate the biochemical hallmarks of TMEs, including acidosis, hypoxia, and dysregulated metabolism.

vacuolar ATPase [26–32].

Therefore, the acidic pHe of TMEs is a result of multiple factors. Poor blood perfusion and the absence of functional lymphatic vessels may intensify acidosis owing to limited clearance of acidic substances from the TMEs. Since tumor acidification has been displayed to be involved with increased tumor invasion and metastases, dysregulated metabolism of carcinogens, and DNA instability, it has been ranked among the most critical hallmarks of TMEs and has become a critical therapeutic target [33].

Several studies have focused on tumor acidity by nanoscale materials with excellent acid/pH-responsive capacity [34,35]. Recently, nanotherapies regulating the acidity of TMEs have gradually been developed. In this section, the latest strategies of nano-DDSs based on the neutralization of tumor acidity are discussed.

2.1. Neutralization by buffer therapy

As a natural alkaline buffer, HCO_3^- continuously increases pH through releasing carbon dioxide (CO_2) ($CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$), thus acting as a potential candidate for increasing the bioavailability and potency of agents inactivated in low pHe [36–38]. Dietary approaches, such as intake of more sodium bicarbonate ($NaHCO_3$), increase systemic pHe and improve therapeutic efficacy [37,39]. However, HCO_3^- absorption in the gastrointestinal tract does not mean sufficient biodistribution to the tumor site [40]. To overcome the difficulty, several nanoscale delivery systems with sustainable buffering capacity have been developed to efficiently target acidic TMEs through the EPR effect [41–48].

Owing to their high payload capacity, the biocompatible calcium carbonate nanoparticles ($CaCO_3$ NPs; nano-$CaCO_3$) have extensively been used for acid-responsive delivery of drugs [49,50]. Som et al. produced a fairly safe size-controllable sub-micron vaterite nano-$CaCO_3$, which was first demonstrated to modulate pHe *in vitro* and *in vivo* with nearly no adverse effects [42]. However, $CaCO_3^-$ associated nanoparticles do not increase pHe in all conditions. Som et al. applied magnetite nano-$CaCO_3$ in a breast cancer model and found that the pHe rebounded and was even lower than the original level at 24 h after injection [51]. Researchers utilized osmotic pumps for persistent infusion and surprisingly observed tumor inhibition. This study attached importance to the way of administration and exact dosage of nanomedicines.

Manganese oxide (MnO_2) also consumes H^+ through the following reaction: $MnO_2 + H_2O_2 + 2H^+ \rightarrow Mn^{2+} + H_2O + O_2$. Therefore, with available metabolites, such as hydrogen peroxide (H_2O_2) and H^+, in the TMEs, MnO_2 elevates pHe by quenching the excessive protons produced by the cancer cells [52,53]. Prasad et al. developed biocompatible and colloidally stable A-MnO_2 NPs and verified their anti-cancer efficacy along with radiotherapy [54]. A rapid increase in pHe was observed from 6.7 to 7.2 after intratumoral injection in a breast tumor model, accompanied by diminished HIF-1α and vascular endothelial growth factor (VEGF). Therefore, MnO_2-based nanoparticles are potential candidates for pHe modulation and require intensive research.

Neutralizing tumor acidity by nanoparticles that generate hydroxide ions (OH^-) represents another promising and efficacious strategy. Gong et al. prepared CaH_2 nanoparticles (nano-CaH_2) by liquid phase stripping method, and these nanoparticles reacted with water to generate abundant OH^- to achieve the neutralization of acidic TMEs [55]. In addition, the byproducts (H_2 and Ca^{2+}) also induced mitochondrial dysfunction and tumor calcification, respectively, leading to enhanced anti-cancer efficacy. Zhang et al. prepared layered double hydroxide nanoparticles (LDH NPs), which disrupted the lysosomes of cancer cells to reduce their transport of excess H^+ produced in glycolysis to the extracellular compartment [56]. Moreover, LDH spontaneously hydrolyzed to produce OH^- to neutralize the acidic TMEs. After the administration of LDH NPs, the pH in tumor tissues exhibited a significant increase and remained elevated for over a week, effectively impeding the proliferation of solid tumors *in vivo* (Fig. 1).

The acidic TMEs also reduce the chemosensitivity by ionizing drugs, making them hydrophilic and lipophobic. Therefore, it is difficult for ionized drugs to pass through the phospholipid bilayer of cell membrane. This biochemical barrier is called “ion trapping”. For example, doxorubicin (DOX), a typical ionizable weak base drug, freely permeates the lipid-based cell membrane [57,58]. However, the uptake is retarded under acidic conditions because weak bases become charged [38,58–61]. To modulate acidic pHe and enhance the effect of DOX, Abumanhal-Masarweh et al. fabricated a 100-nm liposome loaded with $NaHCO_3$, realizing a 21-fold dose in the tumor site compared to that of non-liposomal drug and significant tumor growth inhibition in 4T1 tumor-bearing mice [44].

Using a buffer to directly raise a low pHe in the TMEs has achieved preliminary success, but the related clinical drugs are still a long way off as a number of issues need to be addressed. First, protecting the basic active components from reacting with other bionic acids is of importance to maintain effective concentration at the focal site and reduce systemic adverse effects. Second, it is important to note whether pHe rises asymptotically or sharply. The process for doing this relies on real-time measurements of proton concentration *in situ*. Nanomedicines with modulated speed and degree of alkalization can be obtained by designing adjustable and controllable sizes. Third, neutralization reactions involving one buffer are single and segmented, which may lead to the production of other metabolic acids *via* networked compensatory pathways. Biochemical reactions are complex; thus, one must be aware that pHe just rises tentatively and then rebounds or even drops lower. Lastly, a very high buffering capacity of nanomedicines may also induce only a very small pHe change to achieve an effective tumor-killing alkalinity. Therefore, more unique designs are welcome in nanoscale buffering anti-cancer therapies, and more buffer systems are worth investigating.

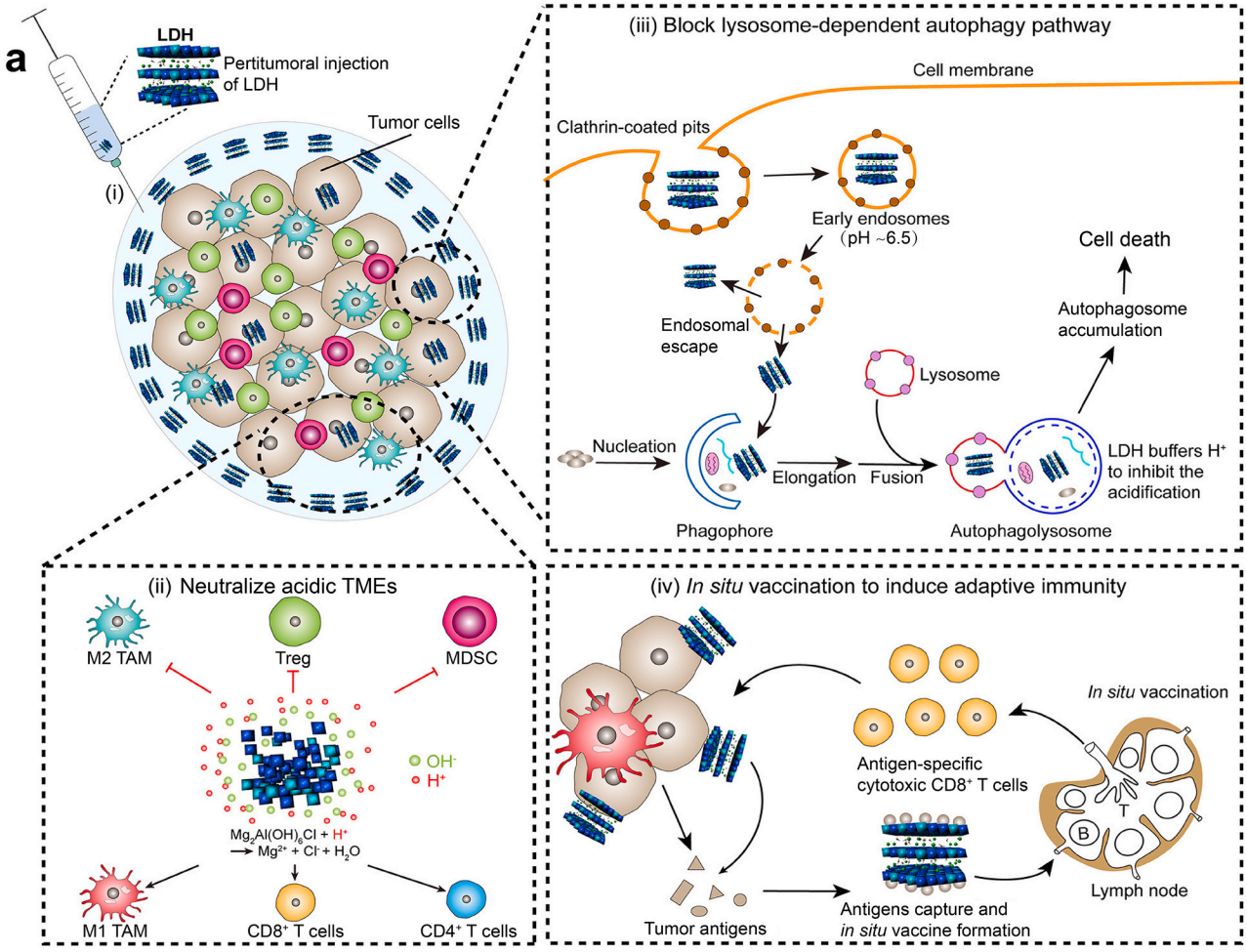
2.2. Modulation of glycolysis and lactate production

Changes in the TME metabolism, such as accumulation of lactic acid mainly produced by glycolysis and exported *via* MCT4, result in acidic TMEs and alter the growth and survival of cancer cells, inducing a malignant phenotype [62,63]. Therefore, several studies have targeted glycolysis and lactate production.

For example, as the rate-limiting enzyme in glycolysis, HK2 plays a crucial role and is closely related to tumor initiation [64–66]. Li et al. prepared HK2-inhibiting liposomal benserazide nanoparticle (Benz NP) to reduce glucose uptake and lactate production [67]. An elevated pH was observed *in vitro*, and tumor growth was significantly inhibited in SW480 colon cancer model. Furthermore, compared to other reported HK2 inhibitors, such as metformin (Met) and 2-deoxyglucose, Benz NP significantly improved the anti-cancer efficacy due to precise targeting and rare toxicity [68–73].

As a representative glucose transporter, glucose transporter 1 (GLUT1) is frequently overexpressed in the cancer cells to maintain active glucose uptake and meet metabolic requirements [74–76]. Therefore, targeting GLUT1 has been demonstrated to be a viable approach to suppress tumor progression, along with decreased metabolites, such as lactate and adenosine triphosphate (ATP) [77–81]. Zhang et al. constructed a unique nanocomposite GNR/HA-DC by embellishing plasmonic gold nanorod (GNR) with a CD44-targeting polymer, and assembling a GLUT1 inhibitor diclofenac (DC) and a hyaluronic acid (HA)-targeting moiety [82]. GNR/HA-DC not only blocked glycolysis and decreased ATP but also downregulated heat shock proteins (HSPs) and enhanced photothermal therapy (PTT). While pHe was not been tested, their results have provided unique ideas for nanomedicines targeting GLUT1.

Emerging evidence has also suggested the immunosuppressive effect of glycolysis and the subsequent acidosis in the TMEs that cause anergy and apoptosis of tumor-infiltrating immune cells [83–87].



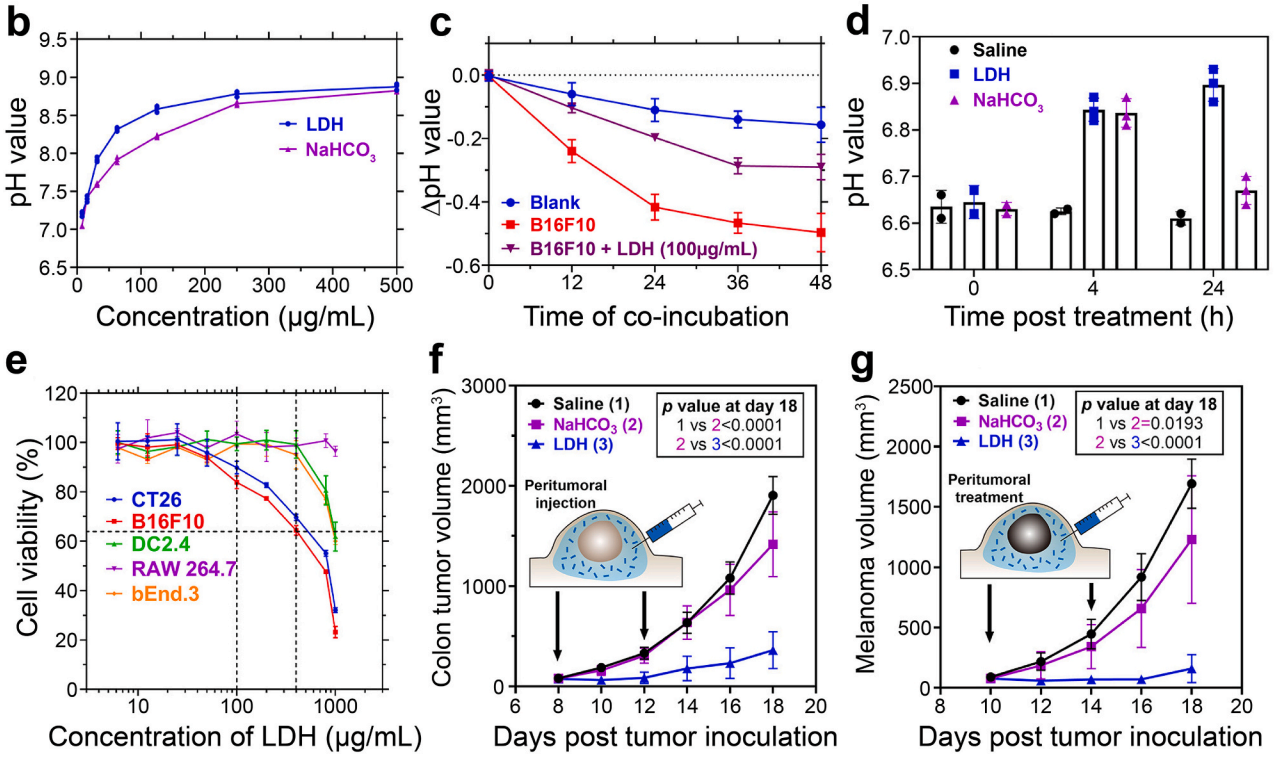


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Fig. 1. LDH NPs regulated acidic TMEs and inhibited tumor growth. (a) LDH NPs regulated the acidic TMEs by generating hydroxide ions and disrupting cancer cell lysosomes, and induced the body to develop adaptive immunity and inhibit tumor growth. (b) pH of deionized water containing LDH NPs (10−500 μg/mL) or $NaHCO_3$ (7.4−370 μg/mL). (c) Effect of LDH NPs on pH of B16F10 cancer cell culture medium (2×10^5 cells per well). (d) Calculated pH value of tumors ($n = 3$) collected from different groups. Data are means ± SEM. (e) Different cancer cells were treated with LDH NPs, and cell viability at the indicated concentrations. Data are means ± SEM. (f) Mean tumor volume of mice with colon tumors under different treatments ($n = 8$). (g) Mean tumor volume of melanoma mice under different treatments ($n = 7$ for saline and $NaHCO_3$ groups; $n = 8$ for LDH group). For f and g, statistical significance was calculated by two-way ANOVA with Tukey's post-hoc test. Reproduced with permission [56]. Copyright 2022, American Chemical Society.

Immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2 tumor-associated macrophages (M2-TAMs), are activated by high lactate levels, leading to the further inhibition of anti-cancer immunity [88–90]. It was inspiringly reported that immune responses were increased when mice were orally fed HCO_3^- or intraperitoneally injected with the proton pump inhibitor esomeprazole [83,87]. Nano-DDSs neutralizing tumor acidity also reverse T cell anergy to enhance anti-cancer effect. For instance, Zhang et al. developed cationic lipid-assisted nanoparticle (CLAN) to silence LDHA, a key enzyme converting pyruvate to lactate in glycolysis [91]. The results showed that the downregulated LDHA, reduced lactate, increased pHe, and subsequently increased infiltration of $CD8^+$ T cells and natural killer cells (NK) and decreased immunosuppressive T cells in the TMEs. Furthermore, reversing tumor acidity is also found to potentiate anti-PD-1 checkpoint blockade therapies. Overall, the clinical potential of this nanostrategy for enhancing T cell-based cancer therapies and combined treatment with checkpoint inhibitors is evident. Huang et al. also developed a dual-target and co-delivery system (Man-LF NP) to simultaneously inhibit glycolysis and reverse immunosuppression [92]. Man-LF NP specifically bound to lipoprotein receptor-related protein 1 and mannose receptors overexpressed in the cancer cells and TAMs. Loaded shikonin, an inhibitor of PKM2 in glycolysis, was reported to reduce lactate production, elevate pHe and produce reactive oxygen species (ROS). It also induced immunogenic cell death (ICD), relieved inhibition of functional T cells, and hindered protumor M2 polarization [93–95]. The loaded JQ1 is an immunomodulator that reduces PD-L1 expression and tumor-infiltrating Tregs [96–98]. In addition, Man-LF NP inhibited tumor growth and significantly prolonged survival time without severe pathologic damage in organs. Multitarget nanomedicines provide an idea for designing single drugs with multiple inhibitory pathways.

Proton pump inhibitors have also proven to be effective in regulating pH. Shabir et al. and Alai et al. successfully developed lansoprazole, a proton pump inhibitor, loaded with nanoparticles for the treatment of acid-related disorders, such as gastric and duodenal ulcerative diseases [99–102]. The designed system showed outstanding capacity for sustained drug release and protected lansoprazole from degradation by gastric acid upon oral administration, which might provide promising opportunities for cancer therapy.

Overall, these studies indicate that targeting glycolysis and/or lactate transportation and production to modulate the acidic TMEs through nanomedicines is an attractive and promising strategy for anticancer therapy. However, there are still some areas to consider and improve moving forward. First, glycolysis is a biochemical reaction that occurs in almost all cells. Thus, it is essential to enhance the targeting ability of nanomedicines and to concentrate their intratumoral accumulation. Second, inhibition of rate-limiting enzymes or key enzymes may induce compensatory metabolic bypasses that alter the cancer cell phenotypes. One possible solution is to upgrade the single-point targeting treatment to multi-point combination therapies. For example, combining inhibitors of multiple enzymes and other active proteins or nucleic acids can be explored. More attention should be paid to improving loading capacity accordingly. Third, given that glycolysis inhibition plays a crucial role in cell metabolism and interacts greatly with the tumor immune microenvironments, it is dangerous to overlook the impact of this kind of nanomedicines on tumor-infiltrating immune cells. An all-round investigation into the activity of other main components in the TMEs may be necessary. Therefore, further research is encouraged to improve the biological properties of nanomaterials in addition to their physical properties due to the complex human microenvironments.

2.3. Inhibition of pH-regulating proteins

To adapt and survive in the acidic and hypoxic TMEs, the cancer cells augment the expression of membrane pH-regulating proteins as a kind of defense. These proteins ensure a slightly alkaline intracellular pH and acidic pHe that favor tumor proliferation and metastases [103,104]. These regulators mainly include Na^+/H^+ exchanger 1 (NHE1), the most common H^+-extruding exchanger on the cancer cell membrane; MCT1 and MCT4, excessively expressed in a wide variety of cancers and responsible for the proton-coupled lactate removal; carbonic anhydrases (CA IX, CA XII), hypoxia-inducible effectors associated with most tumors but absent in healthy tissues and converting CO_2 to H^+ and HCO_3^-; Na^+/HCO_3^- co-transporter (NBCn1/SLC4A7), responsible for intracellular buffering *via* HCO_3^- uptake to the cytosol in exchange for Cl^- and similar to anion exchangers (AEs); and vacuolar H^+-ATPases (V-ATPases), overexpressed in many cancers and associated with different prognostic variables [19,105–110].

These proteins that regulate pH have been the focus of efforts to produce small-molecule inhibitors, which have been examined both *in vitro* and *in vivo*, and some of which have been examined in varying stages of clinical trials [111–115]. Table 1 lists some examples of clinical trials of small-molecule inhibitors that target pH-regulating proteins, including V-ATPase, CA IX, MCTs, NHE1, and NBCs [116–120]. Most were effective in relieving tumor acidosis, thus reducing the cancer cell proliferation, invasion, migration, and metastases, and improving sensitivity to drugs. However, some agents, such as V-ATPase inhibitors (*e.g.*, bafilomycin A and concanamycin A), exhibit high systemic toxicity, and some agents show poor drug accessibility to the tumor site [121]. In addition, as a result of the coordinated action of a number of different pH regulators, the inhibition of one isoform of these proteins may be compensated for efficacy by an enhanced expression or activity in other isoforms. Given these challenges, future applications will combine pH regulator inhibitors with conventional drugs or multiple inhibitors together in non-toxic therapeutic doses. As such, nano-DDSs are an ideal strategy that suits and satisfies complex requirements, especially, given their excellent loading capacity and accurate targeting ability. For example, Amiri et al. developed a nanocarrier of poly (ethylene glycol)-block-poly(lactide-*co*-glycolide) (PEG-PLGA) to encapsulate acetazolamide (ATZ), a substance that blocks CA IX, and combined it with the first-line therapeutic anti-cancer agent temozolomide [122]. They noted an increase in pHe and remarkable cell death in glioblastoma multiforme.

Although only a few studies have currently utilized nanomedicines to target pH-regulating proteins and modulate acidic TMEs, potential targets are abundant and deserve further exploration.

3. Reversal of tumor hypoxia

Tumor hypoxia is defined as a low O_2 concentration and decreased partial pressure of O_2 (PO_2) at the tumor site compared to normal levels. The PO_2 around the tumor tissues in most cancer types is less than 7.5 mmHg and even reaches 0 mmHg, whereas PO_2 in normal tissues is usually over 40 mmHg [123]. Thus, hypoxia is a common feature of TMEs and is closely associated with various factors as follows: 1)

Table 1
Clinical trials of small-molecule inhibitors that target pH-regulating proteins.

pH-regulating protein	Inhibitor	Type of cancer	Trial phase	Clinical trial NCT number	References
V-ATPase	Bafilomycin A1	Solid tumors and/or metastases	Preclinical	–	[116]
	Ilaprazole	Gastric cancer	Phase IV	NCT02638584	–
	Esomeprazole	Esophageal cancer	Phase III	NCT00357682	–
		Breast cancer	Phase II	NCT01069081	–
	Omeprazole	Colorectal cancer	Phase II	NCT02518373	–
		Head and neck cancer	Phase II	NCT02013453	–
	Pantoprazole	Prostate cancer	Phase II	NCT01748500	–
	Digoxin	Head and neck cancer	Phase I/II	NCT02906800	–
	CB-5083	Advanced solid tumors	Phase I	NCT02243917	–
		Lymphoid hematological malignancies	Phase I	NCT02223598	–
	5	Cancer	Phase I	NCT00504790	–
CA IX	U-104	Solid tumors and/or metastases	Preclinical	–	[117,118]
	GC-205	Solid tumors and/or metastases	Preclinical	–	[117,118]
	G250 (Girentuximab)	Kidney cancer	Phase III	NCT00087022	–
		Renal cell carcinoma	Phase III	NCT01762592	–
		Renal cell carcinoma	Phase II/III	NCT02883153	–
	Indisulam	Metastatic colorectal cancer	Phase II	NCT00165867	–
	SLC-0111	Advanced and metastatic solid tumors	Phase I	NCT02215850	–
	DTP-348	Solid tumors, mainly head and neck	Phase I	NCT02216669	–
	3ee9-MMAE (BAY-79-4620)	Solid tumors	Phase I	NCT01028755	–
MCTs	AZD3965	Prostate, gastric cancer, and diffuse large B Cell lymphoma	Phase I/II	NCT01791595	–
NHE1	Amiloride or Ethyl-isopropyl Amiloride	Breast cancer	Phase III	NCT01916317	–
NBCs	S0859, S3705	Solid tumors	Preclinical	–	[119,120]

All the clinical trials in the table can be found on the https://www.clinicaltrials.gov/.

Because the cancer cells proliferate rapidly, the increasing consumption of O_2 exceeds its supply. O_2 concentration decreases, and eventually, an acute and chronic intratumoral hypoxic region is formed in tumors and even near blood vessels [124]. 2) Hypoxic cancer cells secrete VEGF and other pro-angiogenic factors to increase microvessel density. However, these vessels have abnormalities, such as lumen malformation, discontinuity between endothelial cells, and reduced pericyte coverage, inducing hyper-perfusion and hypoxia [125]. 3) Anemia induced by chronic nutrient depletion, chemotherapy, and radiotherapy also leads to a dramatic drop in O_2 supply [126]. Notably, in the early stage of chemotherapy, mitochondrial damage causes decreased O_2 consumption and elevated PO_2, but in the late stage, blood and O_2 supply significantly decrease and eventually induce the hypoxic TMEs [127]. 4) Some adaptive genes, such as CA IX, GLUT-1/3, and VEGF, upregulated by HIF-1α ensure cancer cell survival in the hypoxic TMEs [128–131].

Recently, radiotherapy and photodynamic therapy (PDT) have been used as standard therapeutic strategies in over 50% of cancer patients. However, the resistance to these therapies mainly due to tumor hypoxia has become a new challenge. Because hypoxia reduces oxidation to protect the cancer cells from extensive damage as well as reducing chemical groups, such as –SH, to repair DNA, the killing effects of free radicals generated by radiotherapy are impaired [132,133]. Further, hypoxia can be aggravated by ROS generation during O_2-consuming PDT [134]. With the rapid development of nanotherapeutics in the last few decades, various strategies have been utilized to overcome these difficulties by modulating the hypoxic TMEs, including delivering O_2 to hypoxic sites, generating O_2 locally, and targeting hypoxia-related proteins [135–137].

3.1. Oxygen delivery to hypoxic regions

The direct delivery of O_2 to hypoxic regions using appropriate O_2 carriers or reservoirs represents an innovative strategy to alleviate hypoxia.

3.1.1. Perfluorocarbon (PFC) nanoparticles for oxygen transportation

PFCs, which are comprised of carbon and fluorine atoms, are a class of synthetic compounds that have been investigated for potential applications as artificial blood replacements and contrast agents in ultrasonography, organ preservation, and fluorine magnetic imaging [138–141]. Owing to their good biocompatibility, rapid hydrolysis, high O_2 solubility, low surface tension, and viscosity, PFCs have been extensively used as paradigmatic O_2 carriers for the delivery of O_2 to the hypoxic TMEs [142–145]. Therefore, numerous PFC-based nanotherapeutics have been created to control hypoxia and improve the efficacy of radiotherapy and PDT.

Cheng et al. incorporated a photosensitizer onto PFC nanodroplets to fabricate Oxy-PDT [146]. Injection of this nanodroplet before PDT caused sufficient O_2 release and relieved hypoxia compared to the control. The significant tumor growth inhibition indicated that PDT resistance was overcome in mice. To address hypoxia-associated radio-resistance, platelet inhibition has been explored to increase the permeability of blood vessel and enhance red blood cell (RBC) infiltration and O_2 delivery [147,148]. For example, PFTBA@HSA NP containing platelet-inhibiting perfluorotributylamine (PFTBA) and carrier HSA was fabricated [149]. PFTBA@HSA NP inhibited platelet activation in blood vessels and helped release O_2 upon reaching the hypoxic TMEs, resulting in increased RBCs infiltration and O_2 delivery. This simple strategy had high potential for clinical translation to reverse hypoxia-mediated radioresistance. Moreover, therapeutic modalities combining O_2 delivery systems with other treatments, such as radiotherapy and photodynamic therapy, have been explored. For example, Song et al. modified PEGylated PFC nanodroplets with tantalum oxide, which absorbed and gathered X-ray [150]. They observed enhanced X-ray-induced DNA damage and gradual O_2 release by PFC reservoirs. The promoted efficacy of radiotherapy was further validated *in vivo*. Thus, the PFC/radio- or photosensitizer co-delivery formulation may have promising clinical applications. Zhang et al. developed a photothermally controlled “oxygen bomb" (PSPP–Au_{980}-D) by encapsulating PFC and silicon phthalocyanine (SiPc) cores in a two-layer polymer shell, which was covered with gold nanorod (AuNRs) and DOX coating [151]. Two lasers with distinct wavelengths were utilized to trigger significant O_2 release and generate $^1O_2$, respectively, thus creating a cascading therapeutic effect. Integrated with PDT, PTT and

chemotherapy, this approach synergistically inhibited tumor growth (Fig. 2).

Attempts to relieve hypoxia in the TMEs with perfluorinated compounds are not limited to the field of PFC. Zhang et al. encapsulated IR780 dye into perfluorooctyl bromide (PFOB) nanoliposome to obtain mitochondria-targeted PFOB@LIP-IR780 [152]. PFOB stored and delivered O_2 and prolonged ROS lifetime to enhance PDT effect. Surprisingly, the tumor in 4T1 tumor-bearing mice was eliminated completely and did not reoccur in 18 days afterward, during which time HIF-1α decreased and oxyhemoglobin increased. The nanoplatform is also featured as a contrast agent in computed tomography, photoacoustic imaging, and fluorescent imaging due to the bromine (Br) atom in PFOB. This multifunctional nanoplatform provides a new view of anti-cancer nanotherapeutics by regulating the hypoxic TMEs.

To conclude, PFCs are potent chemically inert synthetic molecules and enlighten researchers about the synthesis of nanomaterials.

3.1.2. RBCs and other hemoglobin-based oxygen carriers

RBCs contain 200−2000 million hemoglobin (Hb) molecules and have been utilized as endogenous carriers to transport O_2 and deliver drugs since 1970 owing to their outstanding biocompatibility, long half-life, and extraordinary loading capacity [153–156]. Therefore, these features may enable RBCs to overcome hypoxia in the TMEs and replenish O_2 during treatments, such as PDT and radiotherapy [157].

For example, to enhance PDT, Tang et al. bound photosensitizer ($ZnF_{16}Pc$)-encapsulated ferritin nanoparticles to the surface of RBCs [158]. Because $ZnF_{16}Pc$ was constantly activated and limited to an O_2-rich zone, photoreaction rate and singlet oxygen ($^1O_2$) production were elevated, and distinct tumor suppression was observed *in vivo*. Another nano-DDS based on RBCs was developed to assist PDT. Wang et al. conjugated chlorine e6 (Ce6)-coated iron oxide nanoparticles to the membrane of DOX-encapsulated RBCs and successfully achieved a magnetic field-enhanced combination therapy with PDT *in vivo* [159]. Therefore, RBCs or the RBC membrane is a promising component for the O_2 delivery of nanomedicines.

Research related to Hb is also inspiring. Wang et al. synthesized the self-assembly of Hb-conjugated micelle and photosensitizer zinc phthalocyanine and demonstrated its outstanding ability to generate ROS in HeLa cells [160]. Another example involved using the photosensitizer Ce6 as the core in the HAS/Hb shell (C@HPOC). Chen et al. found that in 4T1 tumor-bearing mice, C@HPOC released a mass of cytotoxic $^1O_2$ to amplify PDT and induce ICD [161]. A large-scale cell death caused an increased release of danger-associated molecular patterns, including calreticulin, high-mobility group box 1, and ATP, which further activated dendritic cells (DCs), T cells, and NK cells. Due to its ability to boost systematic anti-cancer immunity, C@HPOC was also found to inhibit lung metastases in triple-negative breast cancer models.

Although RBC/Hb-based nanoparticles have good prospects, they have two major limitations. First, reduced elasticity of the RBC membrane possibly caused by the encapsulated agents may result in small vessel blockade and organ damage. Second, undetected antigens on the RBC surface may increase the risk of acute hemolysis. Thus, addressing these two limitations could be a breakthrough for future research.

3.1.3. Ultrasound-triggered oxygen release

Ultrasound-based O_2 carriers have been used to deliver O_2 and serve as ultrasonography contrast agents. They are represented by microbubbles with multiple surface modifications like chitosan, phospholipids, and proteins to sustain O_2 release and enhance foam stability [162–164]. Microbubbles also produce physical and chemical changes following ultrasound triggers, such as high-speed shear stress, powerful shock waves, local high temperature, high pressure, and a vast amount of free radicals [165].

Kwan et al. utilized controllable ultrasound to destroy O_2-carrier microbubbles to release O_2 and simultaneously visualize image-guided O_2 transport [166]. Song et al. developed recycled PFC nanodroplets as an O_2 shuttle for the local ultrasound-triggered delivery of O_2 to regulate the hypoxic TMEs [142]. To relieve chemotherapy resistance caused by hypoxia, Chen et al. established PIO_NP with perfluoropentane core, O_2, and PLGA shell decorated with indocyanine green and paclitaxel (PTX) [167]. PIO_NP immediately released PTX and induced ROS upon exposure to low-intensity ultrasound and near-infrared laser (NIR). In addition, ultrasound-assisted nanosystems reverse other O_2-reliable therapy resistance caused by hypoxia. For example, to address resistance to sonodynamic therapy, Chen et al. constructed a fluorocarbon chain nanoplatform bound with IR780 and O_2 [168]. This nanoplatform was able to induce a high level of ROS triggered by ultrasound to kill PANC-1 cells *in vitro* and *in vivo*. To conclude, ultrasound-assisted nanosystems are worth investigating in combination therapies.

Overall, O_2 delivery may be an effective way to relieve hypoxia and inhibit tumor growth. To create more applicable nanomedicines, there are still some problems to be solved. First, O_2 has a strong chemical activity, and O_2-loaded nanomedicines are prone to react with other reducing substances in circulation, resulting in systemic toxicity. Nanomedicines should be designed with sophisticated packaging and site-specific delivery capabilities. Second, successful O_2 delivery does not mean that only the O_2 concentration is elevated at the tumor site; the level of other oxides may also increase subsequently. Future studies may detect concentrations of relevant substances to gain insight into the chain reactions in O_2 delivery and its long-term effects on tumors. Third, it needs to be determined whether the viscosity, hardness, ductility, and chemical activity of nanomedicines with biological components will change after entering animal models or even bodies of patients. High-resolution imaging systems and advanced analytical methods may be useful in observing these physicochemical properties of nanomedicines *in vivo*. In the future, more types of cells from patients can be explored to carry, reserve, and release O_2 by nanosynthesis technology. Nanomedicines are expected to be safer and release O_2 in a sustainable manner.

3.2. Oxygen generation in hypoxic regions

Although transporting O_2 directly to the tumor sites is simple and effective, it has some limitations, especially the potential toxicity of carrier materials. However, this could possibly be addressed by activating O_2-generating agents.

3.2.1. Catalase-mediated oxygen generation

The levels of endogenous H_2O_2, which can be converted into H_2O and O_2 by catalase, are much higher in malignant tumor cells than in normal cells and are associated with tumor progression. Previous studies have investigated the co-delivery of catalase and photosensitizers or radiosensitizers to enhance PDT/radiotherapy *via* O_2 generation *in situ*. Chen et al. constructed HSA-Ce6-Cat-PTX with catalase, Ce6, PTX, and HSA. The nanoparticles decomposed endogenous H_2O_2 into O_2 in the TMEs by releasing catalase, dramatically alleviating hypoxia to boost the integrated performance of PDT and chemotherapy [169]. Similar nanoparticle constructions became popular, and PTX could be replaced with other antineoplastic drugs. Cheng et al. assembled catalase with DOX precursor (*cis*-aconitic anhydride-linked DOX, CAD), Ce6, and lactobionic acid to get LCC@Ce6-NP [170]. The nanoparticle provided sufficient ROS and O_2 *in situ*, thus decreasing HIF-1α and P-glycoprotein (P-gp) and finally improving the efficacy of chemo-photodynamic therapy. Another investigation by Chen et al. combined catalase with a photosensitizer (methylene blue, MB) in the PLGA core and black hole quencher-3 on the polymer shell to obtain HAOP NP [171]. HAOP NP electively targeted αvβ3 integrin receptor on the cancer cells and constantly produced O_2 to assist photosensitizer-induced $^1O_2$ killing, greatly improving PDT efficacy in hypoxic tumor. Some researchers have installed gatekeepers on nanoparticles to make the content release more synchronized and efficient. Feng et al. assembled catalase and MB

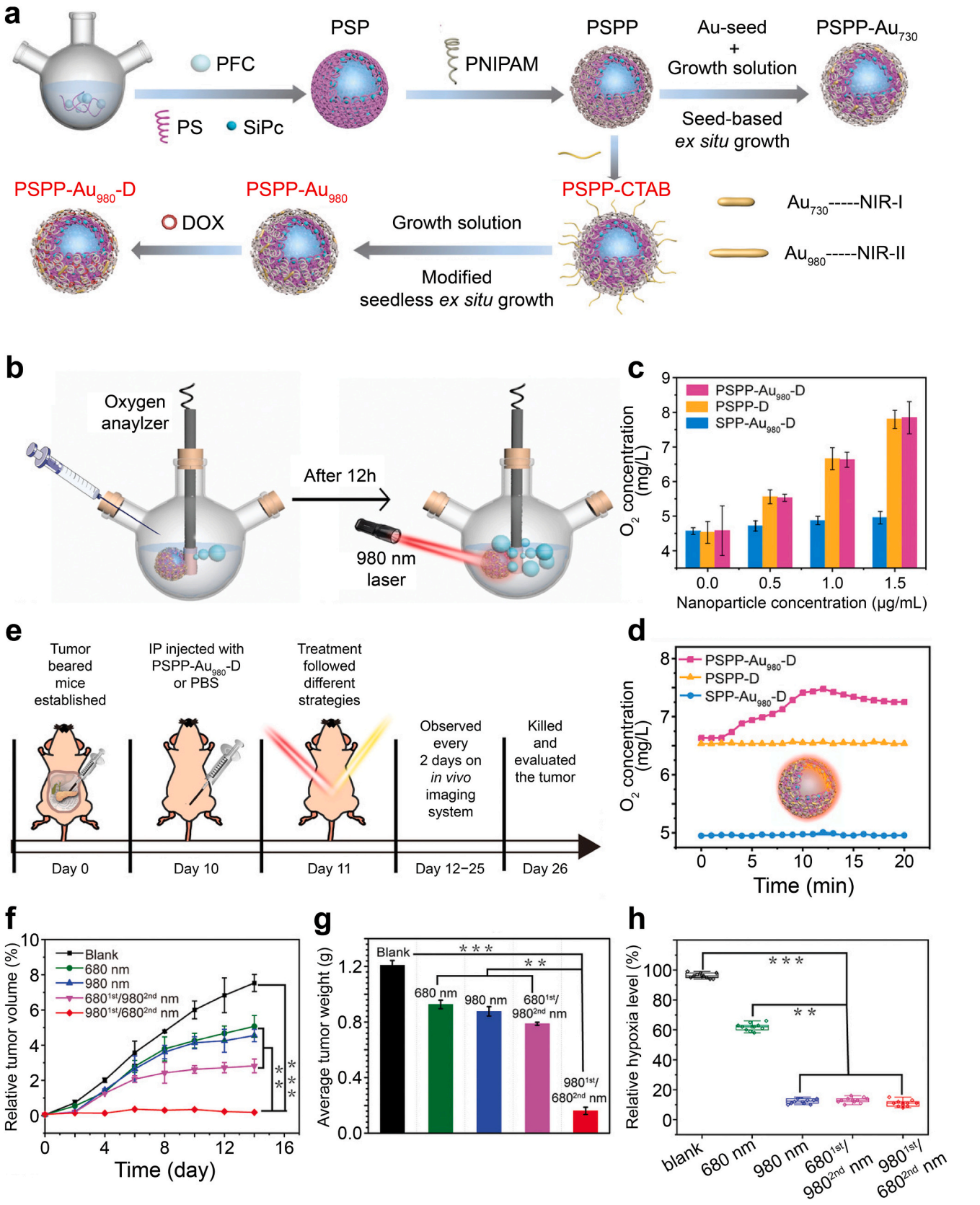

Fig. 2. Photothermal control of O_2 generation by PSPP-Au_{980}-D and triggering of multi-mechanism combined therapy. (a) Synthesis of PSPP-Au_{980}-D or PSPP-Au_{730}. (b) O_2 concentration measured with probe of a portable dissolved O_2 meter. (c) Final O_2 concentration of PSPP-Au_{980}-D, PSPP-D, and SPP-Au_{980}-D ($n = 3$). (d) Changes of O_2 concentration in different groups upon 980 nm laser irradiation. (e) Experimental design *in vivo*. (f, g) Tumor growth (f) and weight (g) curves of different groups ($n = 4$; $^{**}P < 0.01$, $^{***}P < 0.001$). (h) Semi-quantitative analysis of differently treated hypoxic fluorescence areas in histological images ($n = 10$; $^{**}P < 0.01$, $^{***}P < 0.001$). Reproduced with permission [151]. Copyright 2022, Wiley-VCH.

into zeolitic imidazolate framework-8-capped polydopamine nanoparticle (PDA) [172]. In HeLa tumor-bearing mice, it significantly inhibited or even excised the tumor when combined with PDT and PTT. It has also been studies utilizing Ce6-modified glycol chitosan (GC) micelles to amalgamate catalase and MnO_2 (CMGCC). Zhu et al. discovered the prospect of CMGCC in enhancing PDT efficacy in HeLa cells and subcutaneous HeLa tumor [173].

The level of endogenous H_2O_2 varies among different types of solid tumors and is sometimes very limited (10−50 μM) [174,175]. Therefore, another unique study proposed to deliver exogenous H_2O_2 and subsequently generate O_2 with the help of catalase [176]. Continuous oxygenation was achieved by injecting catalase-loaded stealthy liposome (CAT@Liposome) followed by H_2O_2-loaded stealthy liposome (H_2O_2@Liposome). This approach remarkably improved the efficacy of radiotherapy *in vivo*.

Furthermore, several studies have developed catalase-like nanoparticles with anti-cancer activity. Xu et al. used RuO_2 as catalase and formed RuO_2@BSA@IR-808-Br_2 (RBIR), which ameliorated hypoxia and enhanced PDT/PTT in 4T1 tumor-bearing mice [177]. Hua et al. synthesized Pt_2Au_4, an atomically precise alloy cluster with catalase-like activity, which demonstrated an excellent ability to alleviate tumor hypoxia [178]. Ying et al. invented hollow iron oxide nanocatalyst (HIONC)-glucose oxidase (GOD) to improve the efficacy of synergistic therapy of glucose starvation, chemodynamic therapy, and hyperthermia therapy, which possessed catalase-like activity and subsequently inhibited tumor growth in PC3 tumor-bearing mice [179]. Liu et al. exploited the catalase-like properties of platinum (Pt) to create nano-Pt/VP@MLipo and validated its promising effect in 4T1 tumor-bearing mice [180].

Using the decomposition of H_2O_2 to produce O_2 is a worthwhile method. It may be possible to develop more enzyme-induced reactions with similar functions.

3.2.2. MnO_2-mediated oxygen generation

MnO_2 has been a vital component of nanoplatforms as a catalyst and reactant [181–190]. Specifically, MnO_2 reacts with various metabolites in the TMEs, such as H_2O_2 and H^+, and is rapidly reduced to O_2 and Mn^{2+} to simultaneously modulate the acidic and hypoxic TMEs [191,192]. Fan et al. anchored up-conversion nanoprobe (UCSM) to MnO_2 nanosheet to construct a pH and H_2O_2 dual-responsive imaging and O_2-generating nanosystem [188]. The massive generation of O_2 greatly improved the therapeutic efficacy of PDT *in vitro* and *in vivo*.

A combination of MnO_2 and DNA-targeting chemotherapeutic agents has been reported recently. Liu et al. fabricated injectable proenzyme hydrogel (OPeH) composed of MnO_2, the photosensitizer protoporphyrin IXpt (PpIX), cytotoxic proenzyme nanoparticles (PeN), and biocompatible alginate hydrogels [193]. PeN was a derivative from bovine pancreatic deoxyribonuclease I to decompose intracellular DNA and trigger cell death and inhibit metastases by holding up neutrophil extracellular traps. Under 660 nm laser irradiation, a xenograft breast tumor mouse model demonstrated inhibition of tumor growth and even lung metastases. These results provide a unique direction for MnO_2 combination therapy.

Some nanotherapies are combined with cell therapy to further increase drug penetration in the TMEs and reduce adverse effects. Sun et al. encased DOX-loaded mesoporous carbon nanosphere with MnO_2 shell into macrophages (MMDM) to enhance the synergistic effect of chemotherapy and chemodynamic therapy [194]. Based on the ability of macrophages to infiltrate hypoxic areas, MMDM accurately reached the tumor sites and even blind spots with reduced accidental injury of normal cells, and expeditiously decomposed H_2O_2 into O_2. In 4T1 tumor-bearing mice, tumor volume was significantly reduced when MMDM was applied under NIR light irradiation.

Applying MnO_2 nanoplatforms to simultaneously enhance PDT and PTT has become a new trend. Li et al. reacted potassium permanganate ($KMnO_4$) with iridium chloride ($IrCl_3$) to get IrO_2 and modified it with polyvinylpyrrolidone and Ce6 to obtain MIP/Ce6 NP [195]. In HT29 tumor-bearing mice, the tumor was eradicated when MIP/Ce6 NP was injected before 808 and 660 nm laser irradiation; this was much more effective than PDT/PTT alone or conventional administration. Attempts to combine multiple synergistic methods have increased the probability of complete clearance of the cancer cells.

Overall, MnO_2 is a good partner in anti-cancer nanomedicines and requires more attention. Further, it is a versatile substance with anti-acidosis effect, O_2 supply, and immune enhancement. More creative functional combinations with MnO_2 are expected to step into clinical use.

3.2.3. Light-triggered water decomposition for oxygen generation

Photosynthesis converts CO_2 and H_2O to carbohydrates and O_2 upon light absorption. Photocatalytic water-splitting nanocomposites have emerged as advanced tools to overcome tumor hypoxia [196,197]. Zheng et al. created PCCN consisting of carbon dot-decorated carbon nitride (C_3N_4), PpIX, and tumor-targeting Arg-Gly-Asp-modified PEG [198]. Under red light radiation, PCCN exhibited excellent penetrating ability and generated ROS with inappreciable toxicity. In particular, PDT resistance and tumor metastases were inhibited by PCCN *via* the downregulation of HIF-1α and CA IX.

However, discussion about water-splitting materials in cancer treatment mainly focuses on diffusion-limited hypoxia rather than perfusion-limited hypoxia. To simultaneously address these two obstacles, Jiang et al. coated biomimetic ultrathin graphdiyne oxide (GDYO) with iRGD peptide-modified RBC membrane to obtain GDYO@i-RBM nanosheet [199]. GDYO nanosheet possessed sufficient potential for water oxidation and generated $^1O_2$ upon near-infrared irradiation [200,201]. Perfusion-limited hypoxia was further relieved through the dilation of vessels induced by the hyperthermia effect of GDYO, thus resulting in efficient PDT.

Overall, utilizing novel light-mediated water-splitting nanoparticles to create O_2 with exceptional effectiveness is a potential technique to combat tumor hypoxia.

3.2.4. Other oxygen-generating nanoplatforms

Apart from the above three categories, there are O_2-producing nanoparticles with other mechanisms. Chen et al. confined O_2-releasing CuO within the cavities of mesoporous ZrO_2 hollow nanosphere and added 1-butyl-3-methylimidazolium hexafluorophosphate, which improved microwave thermal therapy, DOX, and its release regulator, 1-tetradecanol (PCM) [202]. The nanocomposite was then modified with methoxy poly(ethylene glycol) sulfhydryl to yield IDPC@Zr-PEG. Persistent dissolved O_2 concentration in the TMEs was raised under microwave radiation, and tumor inhibition rate (51.11%–92.14%) was increased, suggesting its huge potential in improving combination therapy efficacy. Zhang et al. used Mn-Cdots to develop RGD-CCmMC/DOX, which generated ROS and further initiated the decomposition of H_2O_2 and alleviated hypoxia in the TMEs [203]. RGD helped locate the tumor by binding to neuropilin-1 and αvβ3 integrin receptors on the cancer cells. RGD-CCmMC/DOX was validated to perform well *in vitro* and *in vivo*. In addition to Cu and Mn, oxides of Ca functioned similarly. Sheng et al. fabricated CaO_2 NP coated with a pH-sensitive protective polymer [204]. In the hypoxic TMEs, the nanoparticle was decomposed to allow water to flow in and react with CaO_2 to generate O_2. Significantly increased PO_2 levels and improved efficacy of PDT were detected *in vivo*. Perhaps, more metal oxides are worthy of further research to obtain the best material.

Additionally, Met, a conventional hypoglycemic agent, is a potent inhibitor of complex I in the electron transport chain in mitochondria and thus increases O_2 by diminishing consumption [205–208]. To overcome PDT resistance, Song et al. injected liposome nanoparticle co-encapsulated with Ce6 and Met into tumor-bearing mice. Oxygenation and therapeutic effects were elevated compared to those of PDT alone [205]. This strategy shows promise in improving PDT efficacy

with clinically approved agents *via* alleviating hypoxia.

In summary, nanomedicines have been widely explored to inhibit tumors by generating O_2 at the tumor site, and this approach is often combined with PDT and radiotherapy. Some details should be carefully reflected as follows. First, if high volumes of gaseous O_2 are created at the tumor site in a short amount of time, local pressure may increase, and the cancer cells or their components may spread quickly to peripheral regions. Second, the metabolic pathways of cells in the TMEs will be altered according to the increase in O_2 concentration, especially the cancer cells with strong adaptability. Third, in combination therapy, the effect of a photosensitizer and the effect of O_2 generation should be organically coordinated in time and space. How to design controllable nanomedicines to achieve optimal therapeutic efficacy remains to be explored, and thus more creative drug combinations are worth exploring.

3.3. Targeting hypoxia-related genes

HIF-1α decomposes under normoxic conditions but translocates to the nucleus and dimerizes with O_2-independent HIF-1β to form HIF-1 in hypoxic cells. In the hypoxic TMEs, degradation of HIF-1α should be incomplete because O_2 supply is transient and cannot resist rapid consumption [209–211]. Only 25%–70% of HIF-1α can be degraded by the currently available tumor oxygenation agents, which allow residual HIF-1α to dimerize with HIF-1β [54,184,212,213]. This process activates multiple oncogenes, such as VEGF, Glut-1, HK2, MDR1, and MMP2, and promotes malignant phenotypes and outcomes [214–216]. Therefore, targeted inhibition of HIF-1α may be a new approach worth trying.

Yuan et al. encapsulated MnO_2 NP with acriflavine to form ROS-responsive ACF@MnO_2 [217]. Acriflavine was gradually transported into the cell nucleus to inhibit HIF-1 transcription and its downstream signaling molecules. ACF@MnO_2 generated O_2 and enhanced sensitivity to radiotherapy by releasing Mn^{2+}. It also significantly decreased PD-L1 and almost doubled $CD8^+$ T cells compared with the control group.

Some HIF inhibitors have already been evaluated in cancer clinical trials [112,218–220]. Nanomedicines have been proposed to overcome adverse effects and enhance the therapeutic effects of HIF inhibitors. For example, CRLX101 containing camptothecin, a potent inhibitor of topoisomerase I and HIF-1α/2α, β-cyclodextrin, and PEG with a size of 20–50 nm realized satisfactory tumor accumulation and intracellular drug release to reduce side effects [221–223]. Although randomized clinical trials of CRLX101 did not show prolonged time without disease progression in patients with advanced renal cell carcinoma, additional trials considered HIF-1α or tumor hypoxia as a vital factor [216,221].

Recently, using siRNA to inhibit HIF-1α has found widespread use in nanosystems, thereby overcoming hypoxia-associated resistance and suppressing the self-rehabilitation of broken double-stranded DNA in radiotherapy and PDT [224–228]. Yong et al. encapsulated HIF-1α siRNA in a radiosensitizer-based Gd- containing polyoxometalate-conjugated chitosan (GdW10@CS nanosphere) and realized preeminent biocompatibility, biodegradability, and strongly condensed positive charge [229–231]. Moreover, intracellular GSH was reduced *via* ROS-generating redox reactions, thus enhancing the effect of radiotherapy. In another study, anti-HIF-1α antibody-conjugated unimolecular polymer nanoparticles loaded with PTX were engineered to improve cancer-targeting therapy [232].

In addition to HIF-1α, other hypoxia-related oncogenes are also potential targets to regulate the hypoxic TMEs. Shi et al. [233]. fabricated HRNP/siCDC20 by self-assembly of the 2-nitroimidazole-modified polypeptide and cationic lipid-like compound to deliver siRNA targeting cell division cycle 20 (CDC20), which was found bioinformatically associated with hypoxia and protumor effect in breast cancer. This nanomedicine was also designed to be triggered by hypoxic conditions. Tumor growth in MCF-7 tumor-bearing BALB/c nude mouse models treated with HRNP/siCDC20 was significantly inhibited without obvious toxicity and inflammatory responses. They detected that silencing CDC20 brought about upregulated cyclin B expression and downregulated Mcl-1 expression, which meant the anti-cancer effect might be due to cell cycle arrest and apoptosis. So CDC20 is a desirably promising target in nanomedicine and deserves more attention (Fig. 3).

Overall, combining radiotherapy, chemotherapy, and PDT with HIF-1α inhibition is promising for modulating hypoxia and addressing therapy resistance. There are also several animal tests to be consulted. Table 2 complements O_2-producing nanoplatforms and their potential applicable treatment regimens by category. Eight nanoplatforms generate O_2 mediated by catalase, six of which are experimented on breast cancer models [234,235–241]. Ten nanoplatforms generate O_2 mediated by MnO_2 and eight are based on metal/metallic oxide [177] [242–259]. In addition to these three categories of O_2-generation nanosystems, mesoporous Prussian blue nanoparticles with hyaluronic acid surface modification (LMWHA-MPB) and hybrid nanozyme@hydrogel doped with Prussian blue nanoparticles incorporated with glucose oxidase also show efficient anti-cancer effects in breast cancer models by generating O_2 in combination therapies [260,261].

4. Regulation of tumor metabolism

4.1. Glucose depletion for starvation therapy

The exaggerated reliance on glucose makes the cancer cells unfavorable when nutrients become scarce. Several nanoscale glucose starvation treatments have been proposed. For example, glucose oxidase (GOx), a natural aerobic enzyme that transforms glucose into gluconic acid and H_2O_2, is most commonly used [262–268]. Zhang et al. synthesized AuNP-PEG-RGD loaded with GOx, and found it killed 80% of breast cancer cells when companied with DOX [269]. AuNP-PEG-RGD-GOx was discovered to even sensitize refractory multidrug-resistant breast cancer cells.

To further increase the efficacy, nanosystems have been combined with other strategies, such as immunotherapy, phototherapy, and gene therapy [262,270–274]. Xie et al. prepared mesoporous silica nanoparticle (MSN) laden with GOx (MSN-GOx) in the cancer cell membrane (B16F10 cells), which helped escape immune clearance, limited the glucose source, and induced ICD of the cancer cells, thus stimulating anti-cancer immune responses [275]. However, the metabolic plasticity of some tumors allows them to maintain survival in the absence of glucose through alternative metabolic pathways. To address this challenge, Meng et al. designed an innovative approach to simultaneously inhibit glucose and glutamine metabolism in the cancer cells [268]. They ingeniously encapsulated rapamycin in glucose oxidase using a defold-fold method, ultimately formulating RAP@GOX-FeS@TCM (RGFM). Glucose oxidase efficiently consumed glucose, while rapamycin administration limited glutamine metabolism and deregulated feedback regulation by mTOR and HIF-1. After systemic administration, there was a notable change in the expression levels of certain genes associated with glucose and glutamine metabolism, such as HIF-1 and SIRT-4 (Fig. 4).

Nanozymes are artificial enzymes that employ nanomaterials to mimic the functions of natural enzymes and exhibit high stability and tunable enzymatic activity, which have recently attracted attention in cancer diagnosis and treatment [276–281]. For instance, Yang et al. integrated GOx and BSA-Ce6 on the surface of MnO_2 NP to obtain core MGB NP [282]. The nanoparticle was coated with RBC membrane (rMGB NP) to reduce the systemic toxicity. On the one hand, O_2 produced by MnO_2 activated GOx for starvation therapy. On the other hand, two main oxidation products, H_2O_2 and gluconic acid, provided MnO_2 with a large amount of H^+ and maximized its enzymatic activity. This crafty structure formed a biochemical reaction cycle to alleviate hypoxia, enhanced starvation therapy, and accelerated ROS generation in PDT *in vitro* and *in vivo*.

Traditional Chinese medicine is also emerging as a glucose

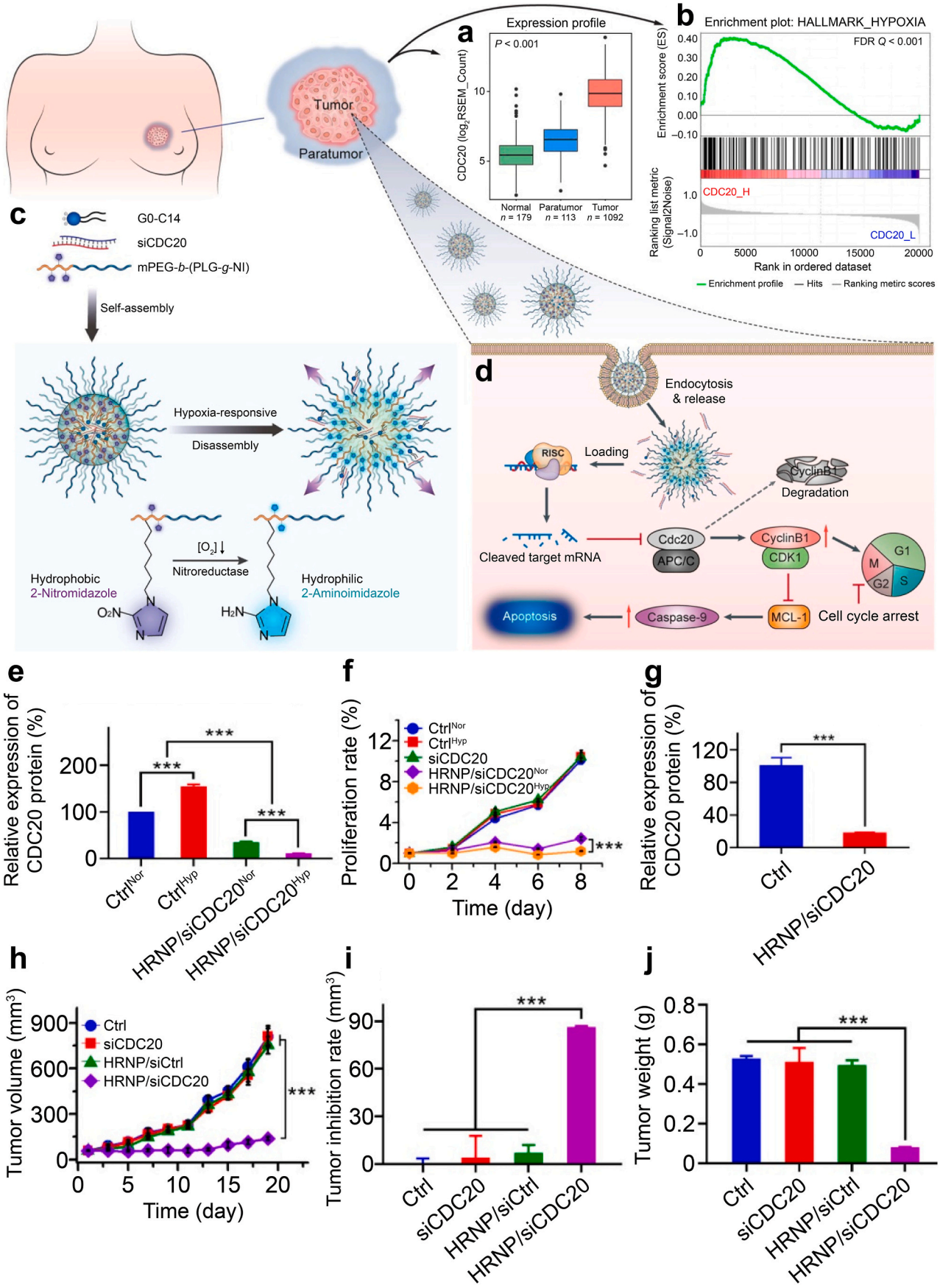

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Fig. 3. Hypoxia-responsive nanoparticle (HRNP) targeting hypoxia-correlated protumorigenic gene (CDC20) improved the effectiveness of treatment for breast cancer. (a) Significant elevation of CDC20 mRNA in breast cancer tissues in contrast to normal and paratumor tissues. (b) GSEA analysis of association between CDC20 and hypoxia in TMEs. (c) Preparation of HRNP/siRNA and mechanism of disassembly in a hypoxic reductive microenvironment. (d) HRNP/siCDC20 delivery into cancer cell cytoplasm to induce G2/M arrest and cell apoptosis for effective cancer therapy. (e) CDC20 expression in MCF-7 cells administered HRNP/siCDC20 under different O_2 levels. (f) Comparison of normoxic and hypoxic MCF-7 cell proliferation after treatment with free siCDC20 or HRNP/siCDC20. As a control group, cells were cultured in growth media devoid of HRNP and free siRNA. Data are shown as mean ± SD ($n = 3$; $^{***}P < 0.001$). (g) CDC20 expression in Ctrl and HRNP/siCDC20 group. (h) Average tumor growth curves across treatment groups. (i, j) Tumor inhibition rate and tumor weight in MCF-7 tumor-bearing mice administrated with Ctrl, siCDC20, HRNP/siCtrl, or HRNP/siCDC20. Reproduced with permission [233]. Copyright 2020, Copyright 2017, American Chemical Society.

Table 2
O_2 generation nanoplatforms for cancer therapy.

Modulation strategies	Therapeutic nanoplatforms	Tumor-bearing mouse models	Applications	References
Catalase-mediated O_2 generation	CAT-THPP-PEG NP	Breast cancer	SPECT imaging, PDT	[235]
	HA-CAT@aCe6 NP	Breast cancer	PDT	[236]
	TaOx@Cat-PEG NP	Breast cancer	RT	[234]
	IF7-ROSPCNP	Breast cancer	PDT-Chemotherapy	[237]
	Ce6-CAT/RPNPs/PEGDA nanocomposite	Colon cancer	PDT-immunotherapy	[238]
	^{131}I-HSA-CAT nanoreactor	Breast cancer	Radionuclide therapy	[239]
	CAT-TCPP/FCS NP	Bladder tumor	SDT	[240]
	CAT@Pt(IV)-liposome NP	Breast cancer	Radio-Chemotherapy	[241]
MnO_2-mediated O_2 generation	C@SMn–Ce6 NP	Breast cancer	NIR-triggered PDT	[242]
	BSA-Au-MnO_2 composite NP	Breast cancer	RT	[243]
	rGO-MnO_2-PEG nanocomposite	Breast cancer	Imaging-guided RT	[244]
	H–MnO_2-GOx-Ce6 NP	Melanoma	Photodynamic-starvation therapy	[245]
	iOCOM nanopod	Oral epidermoid carcinoma	PTT	[246]
	Mn-MOF NP	Breast cancer	PDT	[247]
	PPIX-Lipo-MnO_2 NP	Breast cancer	PDT	[248]
	Albumin-Ce6-MnO_2 NP	Esophageal Cancer	PDT	[249]
	rMGB NP	Breast cancer	Photodynamic-starvation therapy	[250]
	BSA-Bi2S3–MnO_2 nanocomposite	Cervical cancer	RT	[251]
Metal/metallic oxide-based O_2 generation	PCN-224-Pt nanocomposite	Hepatoma	PDT	[252]
	FeSiAuO NP	Cervical carcinoma	Chemotherapy	[253]
	MnTCPP-Hf-FA MOF NP	Melanoma	RT	[254]
	CuTz-1-O_2@F127 NP	Breast cancer	PDT	[255]
	Pt–CuS–P-TAPP NP	Colon cancer	SDT + PDT	[256]
	RuO_2@BSA@IR-808-Br_2 NP	Breast cancer	PTT + PDT	[177]
	Ce6-PEG-Pt(IV)@UCNP	Colon cancer	PDT-Chemotherapy	[258]
	Ir@liposome NP	Breast cancer	RT	[259]
Others	LMWHA-MPB/HMME NP	Breast cancer	SDT-Immunotherapy	[260]
	GOD/hPB@gellan NP	Breast cancer	Photothermal-starvation therapy	[261]

metabolism regulatory agent. Yang et al. ground the crude realgar powder into nanoparticles to improve its solubility and bioavailability [283]. In lung cancer stem cells, as the dose of nano-realgar solution (NRS) increased, glucose consumption decreased. GOx activity and expression of genes related to glucose metabolism in the NRS group was significantly inhibited *in vivo*, and nano-realgar suspension (NRSu) decreased tumor volume even more than cisplatin. The study has inspired researchers that traditional Chinese medicine at the nanoscale level may deserve a try.

Generally, glucose depletion in nanotherapy has good prospects, and we hope that future research will not be limited to GOx. Some points are vital and require attention. First, glucose depletion should be limited to malignant cells and free normal cells, especially effective anti-cancer immune cells. Second, the activity of enzymes is significantly influenced by the environmental conditions, and TMEs are highly heterogeneous among different patients and different lesions. To maximize the effectiveness of enzymes loaded in nanomaterials, it is necessary to conduct in-depth research on the conditions of TMEs and improve the stability of nanomaterials at the same time. Third, the compensatory pathways in the cancer cells in response to metabolic stress are complex, and inhibition of one metabolic pathway may induce drug resistance. Therefore, more research is needed in the field of tumor metabolism reprogramming, and nanomedicines with multiple targets may function better.

4.2. Normalization of amino acid metabolism

4.2.1. Inhibition of metabolism of amino acids nourishing tumors

Glutamine is a non-essential amino acid that can be produced by glutamine synthase to meet cell growth requirements. In the TMEs, the high nutrition demand of cancer cells is fueled by the upregulation of glutamine metabolism. Glutamine is mainly catalyzed by glutaminase (GLS) through glutaminolysis to glutamate and α-ketoglutarate (α-KG). This is proposed to replenish the TCA cycle, also known as glutamine anaplerosis. Besides providing a carbon skeleton for amino acids, the products of glutamine metabolism, such as glutamate, α-KG, and aspartate, serve as nitrogen sources and in turn modulate nucleotide/lipid synthesis and redox balance [284]. Many tumors, such as pancreatic cancer, acute lymphoma, and small cell lung cancer, have shown great sensitivity to "glutamine starvation". Therefore, multiple nano-compounds interfering with glutamine anaplerosis have been created.

For example, combining the GLS inhibitors bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide 3) and compound 968 significantly prolonged survival time by inhibiting cancer cell proliferation and increasing cell death *in vivo* [285,286]. However, their application was limited mainly because of insufficient metabolic stability and restricted solubility [287]. To overcome these obstacles, Elgogary et al. encapsulated BPTES into biodegradable nanoparticles comprising PLGA and PEG to form BPTES- NP [288]. In addition to solving the solubility problems, this method enhanced medication distribution and EPR effect, because PEG prolonged its circulation time. BPTES-NP enhanced tumor growth inhibition *in vivo* and displayed no

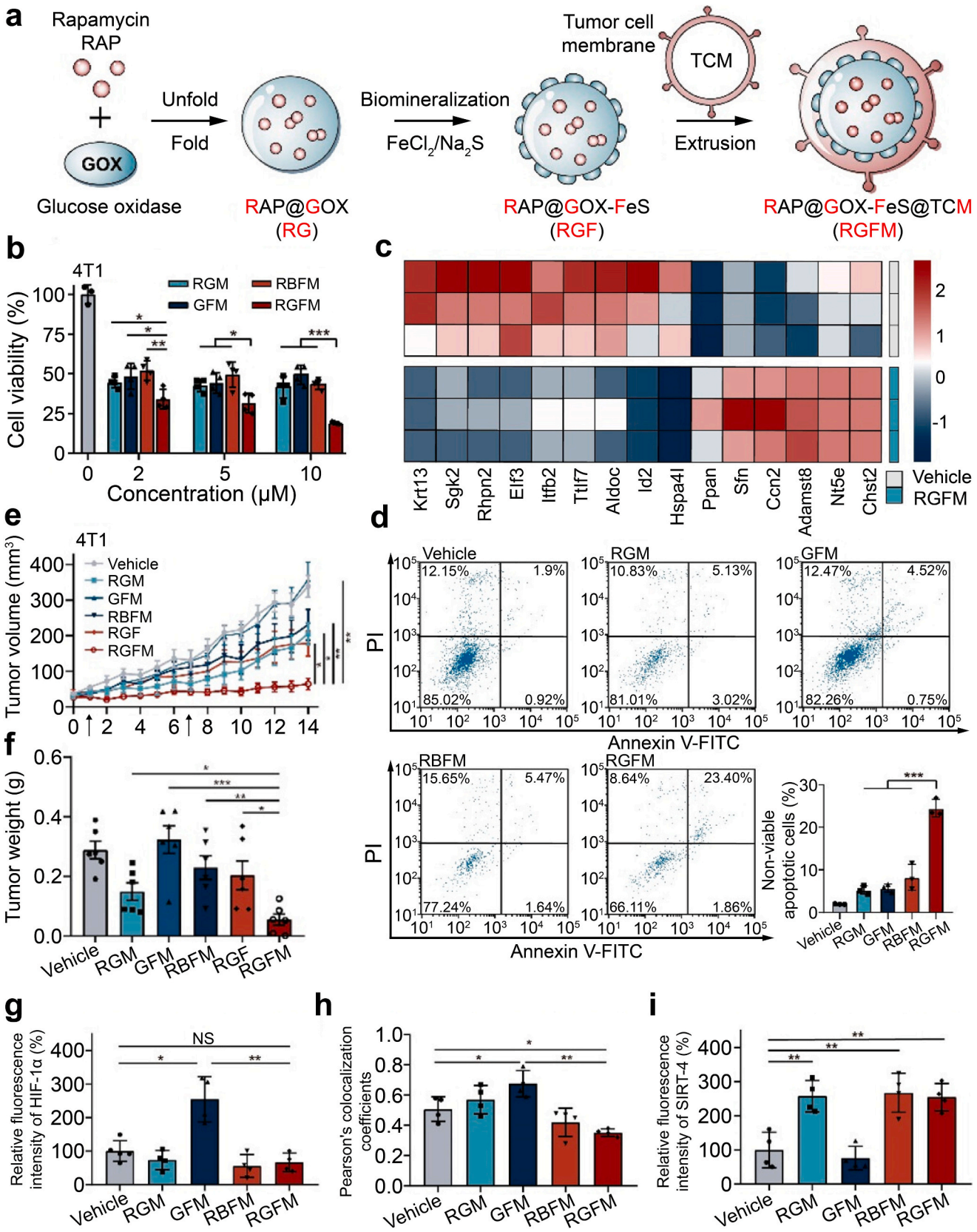

Fig. 4. RGFM simultaneously disrupted multiple metabolic pathways and their feedback regulations. (a) Synthesis of RGFM. (b) Cytotoxicity of RGFM for 4T1 cells ($n = 4$). (c) Heatmap of genes altered by RGFM treatment. Red squares indicated the increased transcription of relevant genes. (d) Apoptosis profile of 4T1 cells after RGFM treatment. (e) 4T1 tumor growth curves after different treatments ([Rap] = 1.0 mg (kg BW)$^{-1}$). Treatments were performed on day 1 and 6. Data were shown as mean ± SEM ($n = 6$). (f) 4T1 tumor weight collected on day 14. (g, h) Quantification of fluorescence intensity of HIF-1α and Pearson's colocalization coefficients of HIF-1α and cell nuclear ($n = 4$). (i) Quantification of fluorescence intensity of SIRT-4 ($n = 4$). Reproduced with permission [268]. Copyright 2024, American Chemical Society.

liver toxicity compared to CB-839, another glutaminase inhibitor presently undergoing clinical trials (phase I/II) among patients with solid malignancies (Fig. 5) [289].

The metabolism of many other amino acids, such as serine and glycine, is also necessary in the cancer cells. Sun et al. reported that the synthesis of serine in hepatoma cells was enhanced in the TMEs upon glucose or glutamine starvation and that the upregulation of related metabolic enzymes was related to the oncogene c-Myc [290]. Moreover, the knockdown of serine hydroxymethyl-transferase or deprivation of exogenous glycine caused cell cycle arrest at the G1 phase in rapidly proliferating cancer cells [291]. Preclinical studies also indicated that limiting serine or glycine intake inhibited tumor growth.

The development of nanomedicines specifically inhibiting the metabolic pathways of amino acids nourishing tumors is still underway and needs more attention in terms of different amino acids.

4.2.2. Suppression of degradation of amino acids attenuating immunity

Recently, an increasing number of studies have attempted to elucidate the relationship between tumor metabolism and immune responses in the TMEs. Metabolic stresses in the immune cells lead to suppressed anti-cancer immunity, one of which is the degradation of essential amino acids.

Arginine, an intermediate product of the urea cycle and a precursor of the protein, polyamine, creatine, and NO, is another essential amino acid that is required for tumor growth [292]. However, arginine metabolism also plays a crucial role in T cell activation and the modulation of immune responses. Previous studies have indicated a strong correlation between arginine degradation *via* catabolic enzyme arginase 1 (ARG1) and suppressed anti-cancer immunity [85,293]. A study demonstrated that arginine supplementation stimulated the proliferation of cytotoxicity T cells and NK cells and the production of effector cytokines in osteosarcoma mice. Besides, combination treatment with anti-PD-L1 antibodies (aPD-L1) enhanced anti-cancer immune responses and prolonged survival time [294]. Therefore, arginine supplementation and its degradation prevention in the TMEs have become promising to re-activate T cell- and NK cell-mediated immune responses. Currently, a clinical trial evaluating the ARG1 inhibitor INCB001158 and its combination with immune-checkpoint-inhibitors is underway and has demonstrated significantly increased tumor-infiltrating $CD8^+$ T cells and NK cells and enhanced production of inflammatory cytokines in the TMEs [295].

Tryptophan is an essential amino acid for T cell proliferation and differentiation and cannot be synthesized de novo. Many types of cells exhibit large levels of indoleamine-2,3-dioxygenase (IDO), an intracellular heme-containing enzyme that catalyzes the first and rate-limiting step in tryptophan breakdown through the kynurenine pathway, such as cancer cells, stromal cells, M2-TAMs, and DCs, and IDO suppresses tumoricidal T cells [296–299]. The accumulation of metabolic product kynurenine increases peripheral Tregs and reduces effector T cells [300]. Fortunately, IDO inhibitors were shown to successfully alleviate immunosuppression in the TMEs and promote the activation of tumor-specific T cells in preclinical models [301]. Following these encouraging outcomes, some IDO inhibitors like Epacadostat have already entered clinical trials [302,303].

To further enhance IDO blockade therapy, nanomedicines have been involved in synergistic strategies [46,304]. Ye et al. proposed a microneedle-based transcutaneous delivery system for αPD-1 and the IDO inhibitor 1-methyl-DL-tryptophan (1-MT) in melanoma [305]. The nanoparticles crossed the stratum corneum and collected in the dermal DC network, thus enhancing the release and retention of immunotherapeutic agents and reducing possible toxicity resulting from leakage into the circulation [306–309]. Moreover, the overexpressed HAase in the TMEs triggered the release of αPD-1 and 1-MT. The synergistic treatment also had potent anti-cancer efficacy and enhanced effector T cell immunity to reduce immunosuppression in the TMEs. Ding et al. designed a hybrid nanopharmaceutical nanoparticle (RPMANB NP) and piggybacked both an IDO inhibitor (NLG919) and a chemo pre-drug (CLB) [304]. The high concentration of phosphate in the cancer cells triggered the collapse of organic platform and caused a burst of drug release. Among them, NLG919 reversed the immunosuppressive TMEs by inhibiting IDO activity, and the chemotherapeutic prodrug was precisely activated *in situ* in the presence of NIR light. By combining tryptophan inhibition with chemotherapy, RPMANB NP significantly suppressed the growth of both localized and distant tumors (Fig. 6).

Although great progress has been made in targeting amino acid metabolism, only a few studies have focused on nano-strategies. Combination with other approaches should also be explored, and prevention of fostering the cancer cells should be considered.

To sum up, regulating amino acid metabolism based on nanomaterials is promising and mainly divided into two categories: hindering the amino acid supply in the cancer cells and amplifying the amino acid supply in effector immune cells. However, there are some pitfalls in the nanomedicine design and administration. First, separation of these two categories of therapies in their respective orbits is critical. It is necessary to strictly prevent the increase of amino acid energy supply to the cancer cells and starve the effector immune cells. Second, the understanding of immune microenvironments of different tumors is not complete, which may lead to incorrect medication. It may be worth trying to add immune-related molecular diagnostics to tumor diagnosis before treatment, which helps select suitable nanomedicines. Third, research should not be limited to glutamine, arginine, and tryptophan, and various essential and non-essential amino acids need to be extensively explored for their pharmaceutical value. In clinical translational studies, the characteristics of human amino acid metabolism and special environmental conditions may be different from animal models and should also be considered. More innovative studies are warranted in the future to regulate amino acid metabolism in the TMEs in terms of all the above concerns.

4.3. Adjustment to lipid/cholesterol metabolism

Ketone bodies, products of lipid metabolism, serve as an energy source produced by liver tissue for extrahepatic tissue. Fearon et al. found that in the nutrient-deficient TMEs, lipid oxidation in stromal cells was accelerated to provide ketone bodies for nearby the cancer cells *via* special transporters [310]. Ketone bodies have been found to be transformed into acetyl CoA to fuel cancer cells through the TCA cycle and oxidative phosphorylation. In addition, to redirect energy production toward anabolic pathways for rich plasma membrane phospholipids and signalling chemicals, the cancer cells often enhance their de novo fatty acid synthesis rate [311]. Previous studies have demonstrated that lipid accumulation switches MDSCs, DCs, and TAMs toward immunosuppressive phenotypes *via* metabolic reprogramming. Thus, lipid metabolism in the TMEs is a potential target to enhance anti-cancer immunity [312–314].

Various inhibitors of fatty acid and cholesterol metabolism have been developed. For example, the sterol *O*-acyltransferase 1 inhibitor avasimibe interferes with cholesterol esterification and increases cholesterol in the plasma membrane of $CD8^+$ T cells to improve their function and proliferation [315]. Yang et al. developed metabolism nano-intervenor (Man-OVA(RSV) NP) and loaded them into a multifunctional hydrogel system (Gel@NP) to interfere with cholesterol metabolism in DC [316]. Rosuvastatin (RSV) disrupted the mevalonate (MVA) pathway in DCs and inhibited the antigenic degradation mediated by the metabolite GGPP/Rab5. Man-OVA(RSV) NP, on the flip side, enhanced the targeting capacity and exhibited sustained drug release properties in DCs. Furthermore, the metabolic reprogramming of DCs effectively revitalized the efficiency of DC-mediated immunotherapy. Therefore, this multifunctional hydrogel delivery system based on the metabolic modulation effectively activated body's anti-cancer immunity (Fig. 7).

Lipid metabolism is also important in modulating EMT and tumor

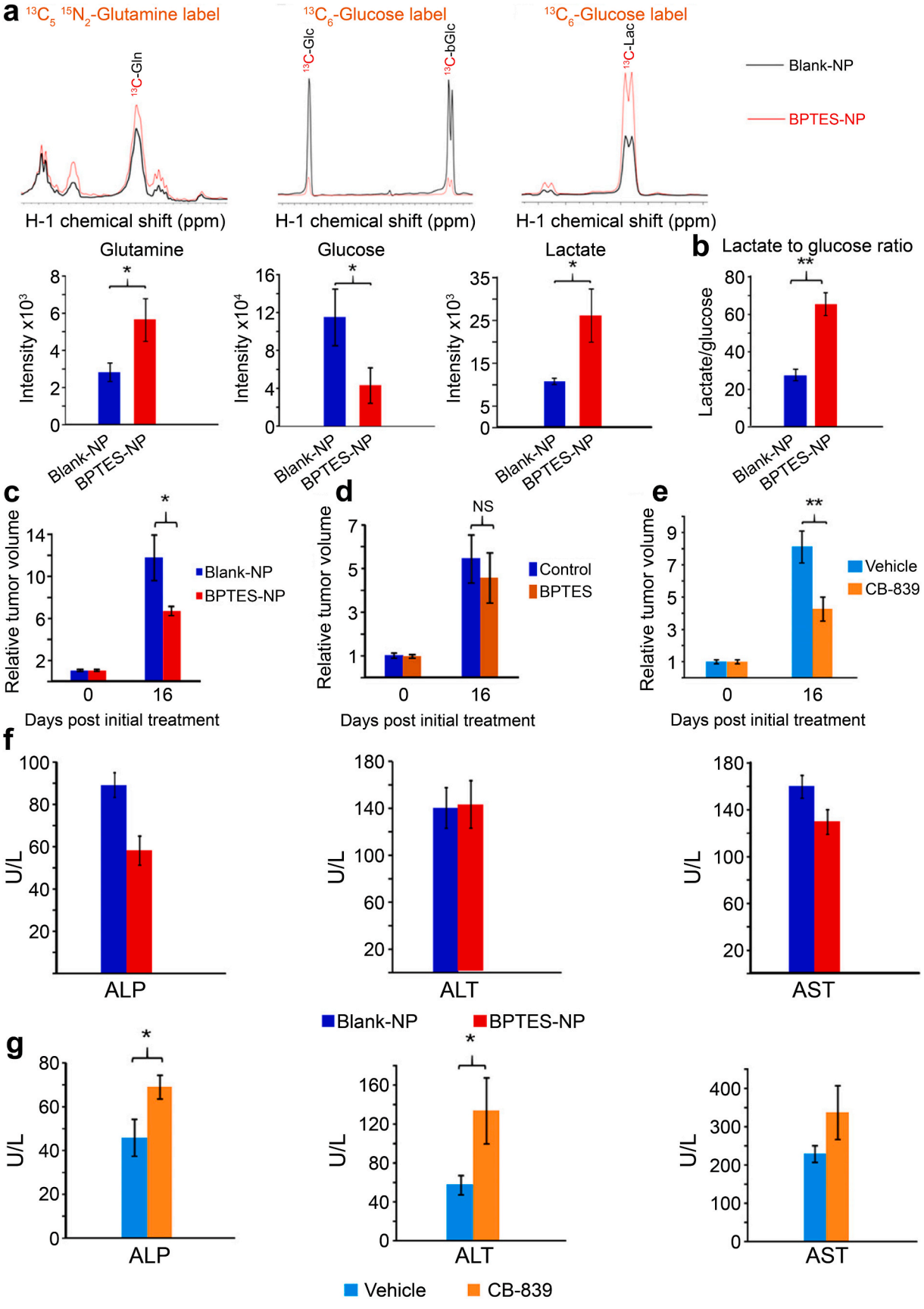

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Fig. 5. BPTES-NP inhibited glutaminase and tumor growth. (a) Mouse tumor metabolomics analysis after BPTES-NP treatment. $^{*}P < 0.05$. (b) Comparison of tumors from mice exposed to blank-NP (blue bars) and BPTES-NP (red bars) for lactate to glucose ratio. Data are shown as mean ± SEM ($n = 5$; $^{**}P < 0.01$). (c) Relative tumor volume of mouse models exposed to BPTES-NP and blank-NP once every three days. Data are shown as mean ± SEM ($n = 8$; $^{**}P < 0.01$). (d) Relative tumor volume of mouse models exposed to 12.5 mg (kg BW)$^{-1}$ BPTES ($n = 12$) or vehicle control ($n = 11$). Data are shown as mean ± SEM. NS, no significant difference. (e) Relative tumor volume of patient-derived orthotopic pancreatic tumors was collected on day 0 and 16 (200 mg (kg BW)$^{-1}$ CB-839, twice per day by oral gavage). Data are shown as mean ± SEM ($n = 8$; $^{**}P < 0.01$). (f, g) Liver response to therapy with BPTES-NP and CB-839. Blood levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are calculated. Data are shown as mean ± SEM ($n = 8$, $^{*}P < 0.05$). Reproduced with permission [288]. Copyright 2016, National Academy of Sciences.

progression [317,318]. Cholesterol-rich lipid rafts are required for TGF-β-directed epithelial plasticity, so cholesterol depletion inhibits the TGF-β-induced EMT [319]. Jin et al. encapsulated the cholesterol regulator simvastatin and PTX into liposomes modified with hairpin-structured peptides that could be cleaved by the TMEs-associated protease legumain [320]. In lung adenocarcinoma mice, simvastatin repolarized M2-TAMs to M1-TAMs *via* down-regulating cholesterol-associated LXR/ABCA1 and remodeled the TMEs by inhibiting TGF-β.

Cholesterol metabolism-targeting therapy is also combined with radio frequency therapy. Singh et al. synthesized high-density lipoprotein mimicking magnetic nanostructure (HDL-MNS) to diagnose and treat B-cell lymphoma [321]. The possible mechanisms involved cholesterol depletion-induced cell death and thermal-activated immune responses. HDL-MNS recognized and bound to scavenger receptor type B1 and resulted in cholesterol efflux and depletion. The MNS core was able to convert energy from the radio frequency field to heat and trigger further innate and adaptive anti-cancer immune responses by increasing HSPs.

Therefore, these studies are of great value and provide a scope for future lipid metabolism-targeting therapies. However, some problems deserve attention. First, more malignant phenotypes of tumors need to be analyzed together with lipid and cholesterol metabolism, apart from EMT and immunosuppression. Second, adipose is very important in tumor progression. The plasticity of cancer cells may be utilized to transform the cancer cells into post-mitotic and functional adipocytes, which may be achieved through nanotechnology in the future [322]. Third, lipids are the main components of biological membranes, and these nanomedicines need to be carefully balanced in terms of biosafety to avoid severe toxicities. It is urgent to improve the understanding of lipid and cholesterol metabolism reprogramming in tumors and its dynamic impact on the TMEs, and to discover more potential targets suitable for nanomedicines.

4.4. Interference with nucleotide synthesis

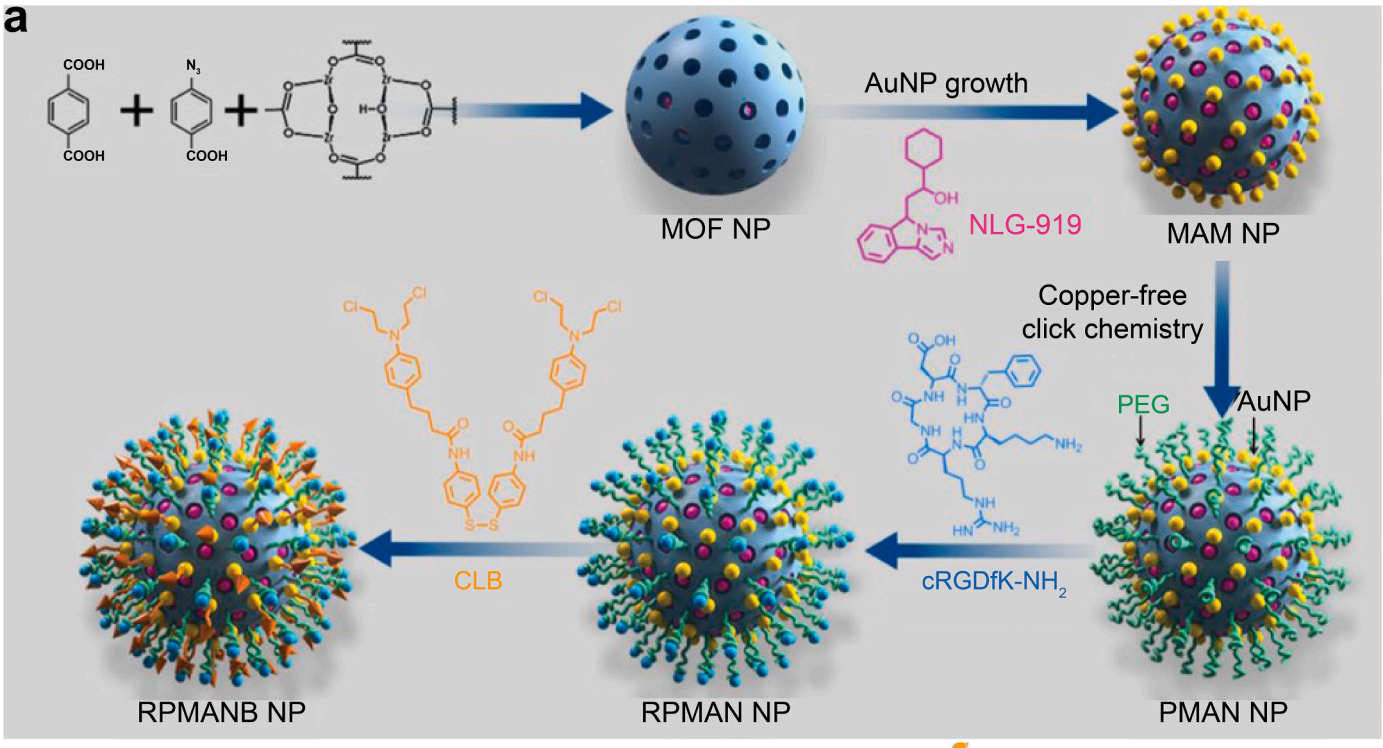
DNA and RNA synthesis is more active in tumors than in normal tissues. Reducing the decomposition of nucleic acids in the tumor complicates things, causing very high amounts of DNA and RNA as materials for the rapid proliferation of cancer cells. 5-Fluorouracil (5-FU) is one of the most widely used chemotherapeutic and antimetabolite drugs for breast cancer, head and neck cancer, and aerodigestive cancers [323]. 5-FU is transported into cells *via* nucleoside transporters and can be converted into four active metabolites, including fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate, fluorouridine triphosphate, and fluorocytidine triphosphate. They interfere with the nucleotide metabolism pathway to exert cytotoxic effects by suppressing DNA synthesis and disrupting RNA processing [324–327]. However, the application of 5-FU is restricted because of systemic toxicity and unfavorable efficacy when administered alone. To overcome these problems, nano-strategies in combination with other agents have been developed. McEwan et al. attached 5-FU on an O_2-loaded microbubble (O_2MB) platform (O_2MB-5FU) for pancreatic cancer treatment and validated its efficacy *in vivo* [328]. Sheng et al. incorporated magnetic microbubble (MB) consisting of an iron oxide core and a lipid coating into the shell to form MagMB [329]. MagMB only exerted an effect at the target site in the presence of an external magnetic field and significantly promoted cell apoptosis when ultrasound was added. These findings demonstrate the promise of combined sonodynamic and antimetabolite nanotherapies.

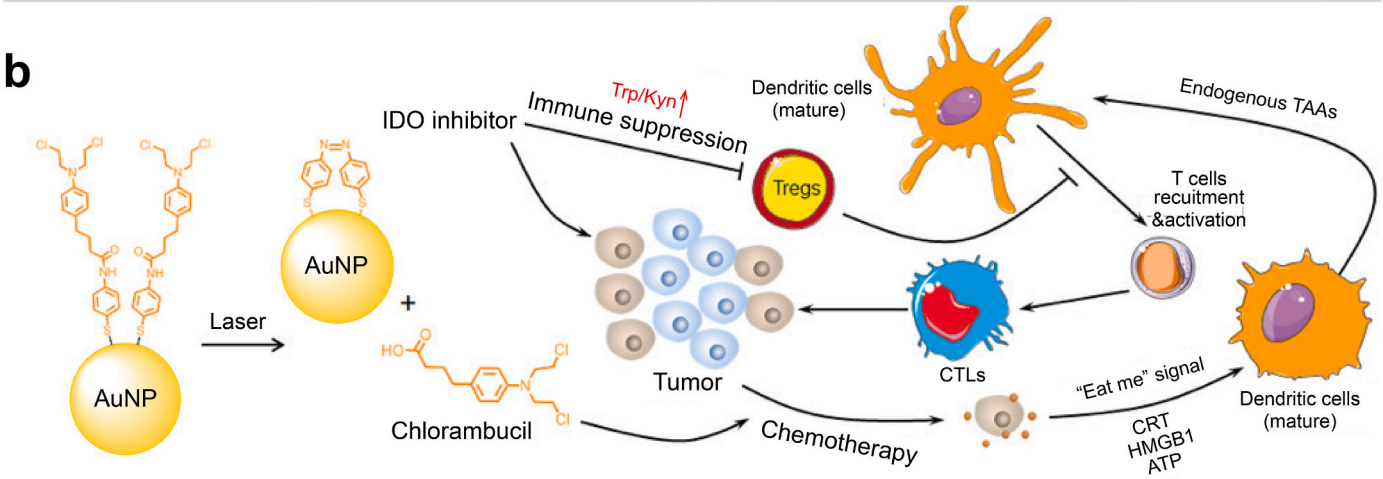
Besides 5-FU, other cytotoxic drugs targeting nucleotide synthesis are also increasingly gaining attention. Cheng et al. took advantage of endogenous serum albumin to load micellar nanostructures of lipid-conjugated floxuridine homomeric oligonucleotide (LFU20) [330]. Floxuridine inhibited deoxythymidine synthase and prevented deoxythymidine methylation into deoxythymidine. In the cancer cell lysosomes, LFU20-albumin complexes decomposed and released active floxuridine monophosphate. Shrinkage in tumor volume was also detected *in vivo* (Fig. 8). This study encouraged researchers to utilize different biological vectors in human bodies.

There are numbers of studies on nanoscale strategies targeting metabolism. Table 3 supplements some results of representative studies not mentioned above for reference and comparison in terms of glucose depletion, amino acid metabolism, lipid/cholesterol metabolism, and nucleotide synthesis [265,266,331–340]. In brief, nanomedicines for regulating nucleotide synthesis are promising but still in the primary stage. Most of the existing nanomedicines are upgrades of traditional chemotherapy drugs. Future research should ideally move beyond the original framework to innovative use and combination of nano-components rather than just structural optimization.

5. Conclusion and perspectives

Studies on anti-cancer nano-formulations have paid increasing attention to the TMEs, recognizing their influence beyond that of the cancer cells alone. Although the physical and chemical features of TME limit the efficacies of traditional anti-cancer treatments, they also provide targets for the development of more effective therapies. The advantages of anti-cancer nanotherapeutics for modulating the TMEs can be summarized as follows: 1) Local treatment: TMEs play a crucial role in tumor growth and metastases. Nanomaterials can be designed to selectively regulate the TMEs, such as inhibiting tumor angiogenesis and modulating the tumor immune microenvironments, thus achieving local treatment and blocking tumor growth and metastases. 2) Improved drug delivery: The complexity of TMEs often limits drug delivery and efficacy. Nanomaterials serve as carriers to enhance drug delivery efficiency in the TMEs by improving drug solubility, stability, and targeting, thereby improving therapeutic effects. 3) Overcoming multidrug resistance: Various factors in the TMEs, such as interactions between cancer cells and changes in the extracellular matrix, tumor acidity and hypoxia lead to multidrug resistance. Nanomaterials can be designed with multiple functions, such as reversing multidrug resistance and inhibiting tumor stem cells, to help overcome this challenge. 4) Achieving combination therapy: The complexity of TMEs requires the use of multiple treatment modalities for combination therapy. Nanomaterials simultaneously carry different types of drugs, genes, or immune modulators to achieve multifaceted therapeutic effects and improve the overall treatment outcome. 5) Real-time monitoring and feedback: Some nanomaterials themselves have imaging or biological detection capabilities for real-time monitoring the changes in the TMEs and adjusting treatment strategies through feedback mechanisms to achieve personalized therapy. In summary, by targeting the characteristics of TMEs, nanomaterials provide more precise and effective tumor treatment strategies, offering unique hope for cancer therapy.





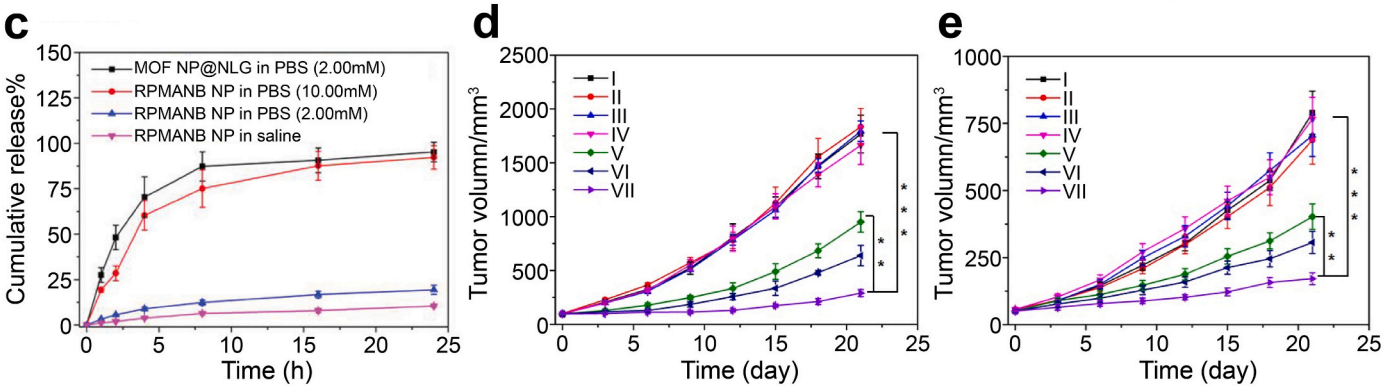


Fig. 6. High concentrations of intracellular phosphate triggered RPMANB NP to release IDO inhibitor and chemotherapeutic agent for combination therapy. (a) Preparation of hybrid nanomedicine RPMANB NP with the ability to co-deliver a CLB and an NLG919. (b) Anti-cancer immune response and chemo-immunotherapy by RPMANB NP. (c) Release of NLG919 from MOF NP@NLG919 or RPMANB NP in saline and PBS containing different phosphate concentrations. (d, e) Growth curves of primary tumors (d) and distant tumors (e) of 4T1-tumor-bearing mice after different treatments ($n = 5$; $^{**}P < 0.01$, $^{***}P < 0.001$). I: PBS; II: NLG919; III: RPMAB NP; IV: chlorambucil; V: RPMAB NP+L (785 nm, 50 mW cm^{-2}, 30 min); VI: RPMANB NP; VII: RPMANB NP+L (785 nm, 50 mW cm^{-2}, 30 min). Reproduced with permission [304]. Copyright 2021, Wiley-VCH.

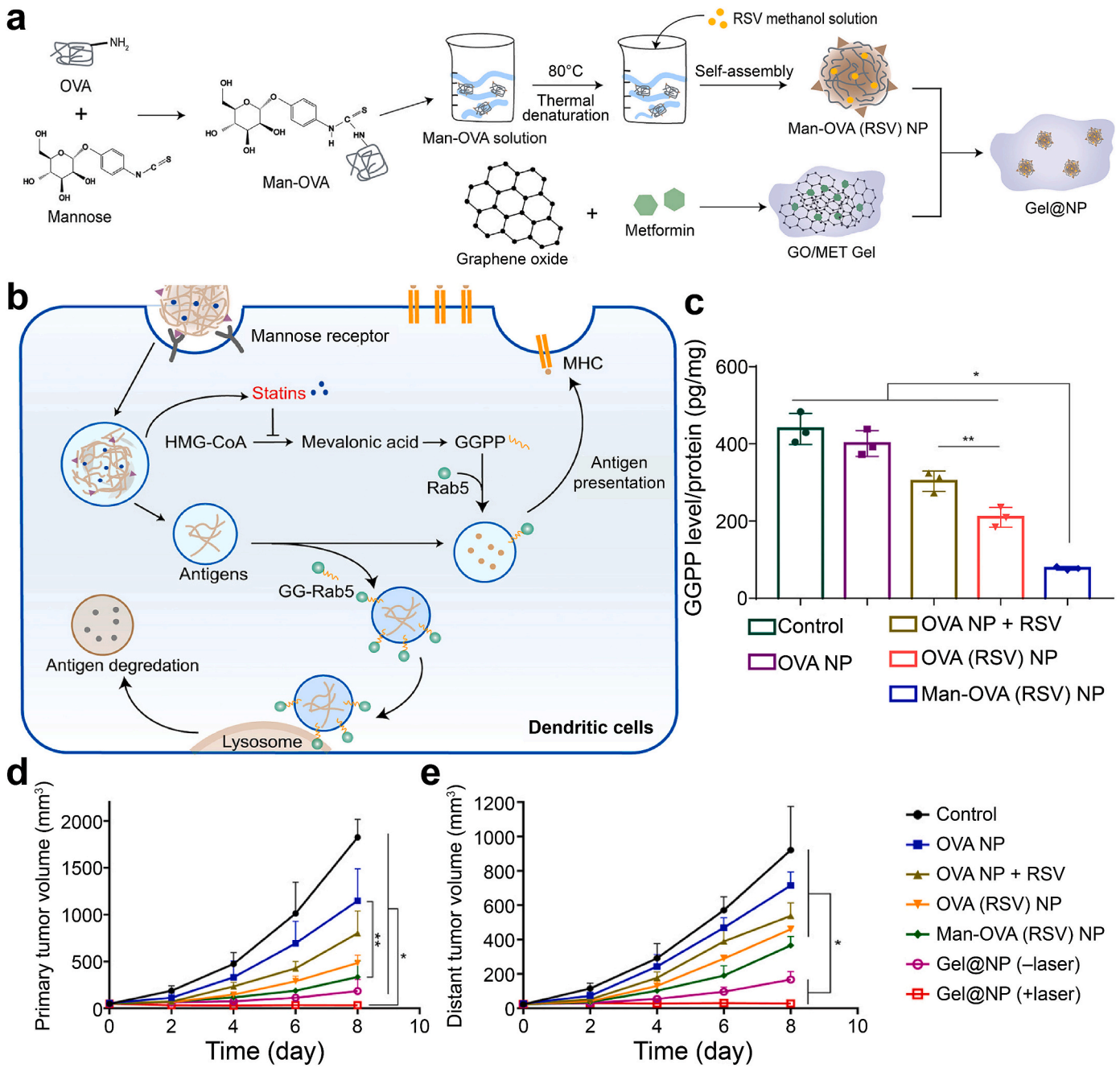


Fig. 7. Man-OVA(RSV) NP inhibited DC cholesterol metabolism and increased tumor antigen presentation, thereby enhancing the body's anti-cancer immunity. (a) Preparation process of Gel@NPs. (b) Man-OVA(RSV)-mediated antigen degradation and antigen presentation *via* interfering with the metabolic MVA pathway. (c) GGPP level in BMDCs with different treatments. (d, e) Changes of primary (d) and distant (e) tumor volume in C57BL/6 ($n = 5$). Reproduced with permission [316]. Copyright 2022, Elsevier.

The preceding sections have delineated the latest strategies and trials in emerging nanotherapeutics especially modulating biochemical hallmarks of TMEs, represented by tumor acidosis, hypoxia, and dysregulated metabolism. Remarkable progress has been made in this field, yet several issues remain unresolved. First, a deeper understanding of TMEs and the physical and chemical properties of cancer cells is essential for the advancement of fabrication techniques. More ideal targets remain to be explored. For example, mutations in oncogenic KRAS, an important regulator of glutamine metabolism, have been identified in more than 90% of pancreatic ductal adenocarcinoma (PDAC) patients [359]. Therefore, nanotherapeutics that modulate the TMEs by selectively blocking glutamine metabolism have been developed and demonstrated excellent anti-cancer effects against KRAS-mutated PDAC [288]. Second, although nano-strategies targeting dysregulated metabolism significantly inhibit the growth and proliferation of cancer cells, they can be a double-edged sword. Such interventions may exacerbate nutritional stress in the tumor vicinity, causing severe adverse effects and tumor metastases, necessitating a rational design of nanomaterials with high targeting ability to enhance selectivity. Third, considering the complexity of cancer, a combination of multidimensional therapeutic modalities might be required. For example, a single nano-DDS can be designed to simultaneously neutralize tumor acidity and relieve tumor hypoxia. Moreover, targeting more than one metabolic pathway is also beneficial in alleviating the impact of tumor metabolic plasticity on therapeutic efficacy [268]. A multifaceted strategy that targets both the physical and chemical properties of TMEs, possibly in conjunction with

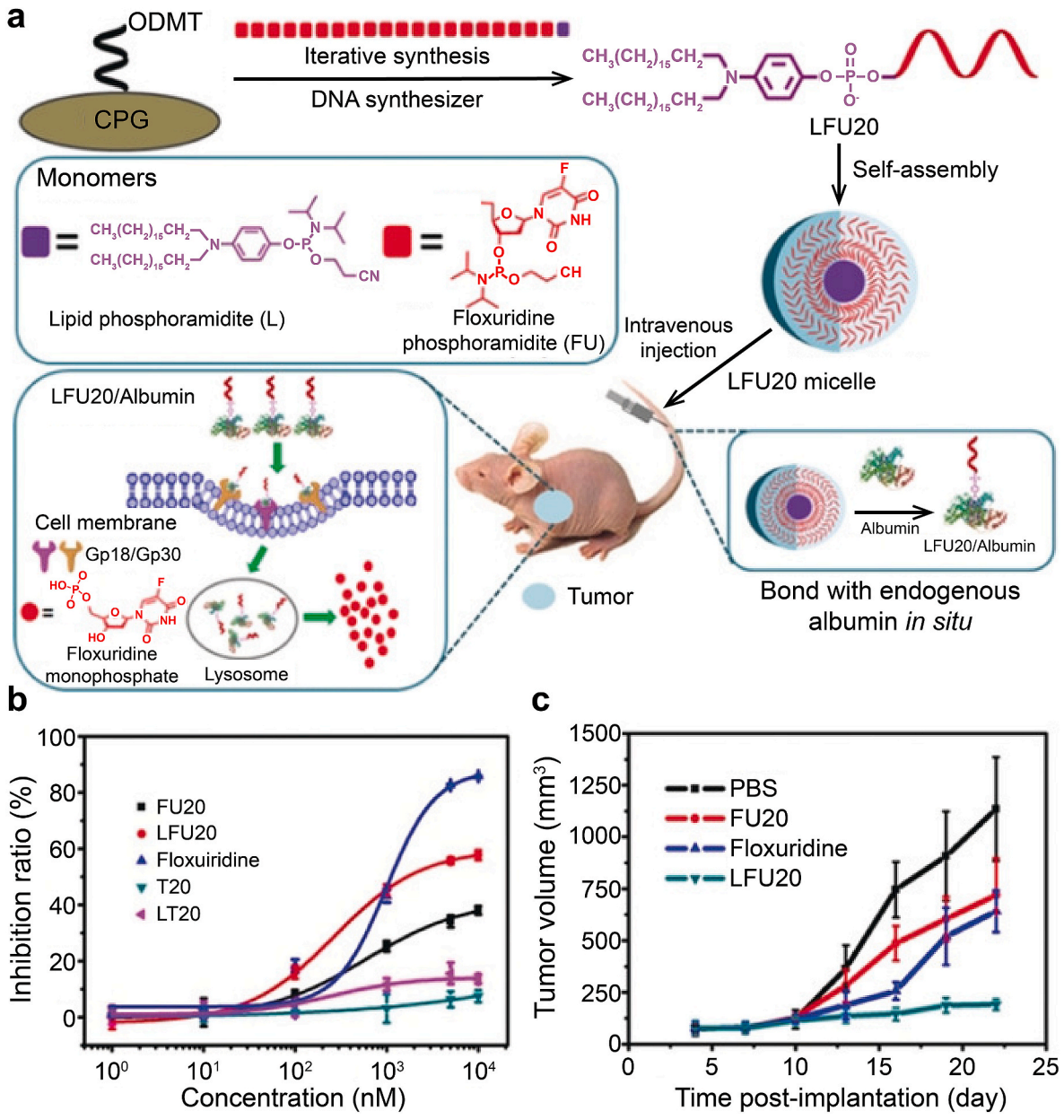


Fig. 8. LFU20 accumulated in tumors and released cytotoxic fluorouridine phosphate to inhibit cancer cell proliferation. (a) Solid-phase synthesis, self-assembly, and the subsequent cancer therapy of LFU20. (b) Inhibition ratios of different treatments to HeLa cells. Samples were diluted with DMEM culture medium (10% FBS) to the corresponding concentration, followed by addition to 96-well plates. Cells were cultured for an additional 48 h prior to cell viability assay. The concentration of free floxuridine is twenty-fold higher than that of the label on the X axis. (c) Tumor volumes of different treatments groups. Reproduced with permission [330]. Copyright 2018, German Chemical Society.

tumor vessel normalization strategies, could be more effective. In addition, combination with other treatments, including chemotherapy, radiotherapy, and PDT, may further mitigate adverse effects and optimize outcomes. It is imperative that research efforts not only demonstrate efficacy but also establish a clear therapeutic superiority. Fourth, in addition to the tumor acidity, hypoxia, and abnormal metabolic microenvironments that we mainly discuss above, the regulation of metal ions' concentrations within the TMEs, which play an important role in tumor progression, has also shown promising therapeutic advances [360]. Taking calcium ions as an example, calcium overload has been confirmed to induce cancer cell death through mechanisms, such as mitochondrial damage and biomineralization [361,362]. The modulation of Mg^{2+} concentration has been found to activate CTLs and induce an anti-cancer immune response [363]. Furthermore, the accumulation of iron ions not only induces ferroptosis but also leads to oxidative stress and DNA damage through participating in the Fenton reaction, which ultimately results in cell death [364,365]. Similar as iron ions, copper ions induce apoptosis by facilitating free radical generation and cuproptosis [366,367]. Besides, metal ions like Mn^{2+} and Zn^{2+} also exhibit capacities to inhibit tumor progression [368,369]. Metal-based nanoplatforms have been validated as efficient in suppressing tumors in multiple studies [370–374]. Fifth, in the pursuit of clinical translation, it is critical to acknowledge the substantial differences that exist between animal models and human physiology, especially in terms of tumor complexity, metabolic alterations, and drug pharmacokinetic properties [375–377]. The development of more representative preclinical models and the initiation of clinical trials that address these discrepancies are of paramount importance. Finally, improving the availability and convenience of nanomedicines represents a critical focus for the subsequent phases of research.

Table 3
Nanoscale strategies for targeting metabolism.

Targeted metabolic pathway	Therapeutic nanoplatforms	Tumor-bearing mouse models	Applications	References
Glucose depletion	IrRu-GOx@PEG NP	Breast cancer	Starvation and oxidative therapy	[331]
	PAAO-UCNP-GOx nanoreactor	Breast cancer	Starvation and phototherapy	[332]
	BGPO NP	Breast cancer	Starvation and PTT	[333]
	GOx-MnCaP NP	Breast cancer	starvation and chemodynamic therapy	[334]
	HMBRN-GOx/TPZ NP	Glioma	Starvation and enhanced bioreductive chemotherapy	[335]
	P@Pt@P–Au-FA NP	Breast cancer	Starvation and PDT	[336]
	CMSN + GOx NP	Melanoma	Starvation and immunotherapy	[337]
	HMSNs-GOx-Ce6@PFC-CPPO@C	Colon cancer	Starvation and PDT	[266]
	Fe_5C_2-GOD@MnO_2 NP	Cervical carcinoma	Starvation and enhanced anti-cancer therapy	[340]
	TGZ@eM NP	Colon cancer	Starvation and enhanced bioreductive chemotherapy	[338]
	PHPBNs-S-S-HA-PEG@GOx	Hepatoma	Starvation and PTT	[265]
	COF@GOx&CAT	Breast cancer	Starvation and PDT	[339]
	P/GAu NV	Melanoma	Starvation and hypoxia-activated gene therapy	[283]
Amino acid metabolism	OX/IND-MSNP	Pancreatic ductal adenocarcinoma	Immunotherapy	[341]
	aPD-L1@HC/PM NP	Colon cancer	Immunotherapy	[342]
	NLG919@DEAP-^{D}PPA-1 NP	Breast cancer	Immunotherapy	[343]
	$CLAN_{siIDO1}$ NP	Colon cancer	Chemo-immunotherapy	[344]
	aPD-1/1-MT-loaded microneedle	Melanoma	Immunotherapy	[305]
	EAPV	Colon cancer	PDT and Immunotherapy	[345]
	IND@RAL NP	Breast cancer	PDT and Immunotherapy	[346]
	Dox/POEG-b-PVBIND NP	Breast cancer	Chemo-immunotherapy	[347]
	man-GNR-siIDO NP	Lewis Lung carcinoma	Immunotherapy	[348]
Lipid/cholesterol metabolism	Nano-ORL	Prostate and breast cancer cell lines	Metabolic therapy	[349]
	Nano-formulated peptide pACC1	Breast cancer	Metabolic therapy	[350]
	DOX-MNP+Avasimibe	Breast cancer	Metabolic and chemotherapy	[351]
Nucleotide synthesis	Modified mRNA LNP	Melanoma	Immunotherapy	[352]
	DTX-siRNA-CH NP	Breast cancer	siRNA and chemotherapy	[353]
	Au NR	Lung cancer cell lines	Metabolic therapy and anti-cancer drug screening	[354]
	AMO-LGdH NP	Breast cancer cell line	microRNA therapeutics	[355]
	3WJ-EGFRapt/anti-miR-21 NP	Breast cancer	microRNA therapeutics	[356]
	LFU20/albumin micelle	Cervical carcinoma	Metabolic and chemotherapy	[330]
	D/R/SNC	Cervical carcinoma	NIR-guided siRNA and chemotherapy	[357]
	ssDNA and siRNA loaded NS-PLL	Lung cancer cell line	NIR-guided siRNA therapy	[358]

Despite the present issues and challenges, nanotherapeutics that modulate the TMEs have shown promising outcomes in combination treatments to target multiple aspects of the TMEs, enhanced treatment efficacy, and reduced systemic toxicity. Further optimization and collaboration among scientists, clinicians, and industry partners, as well as investment in clinical trials, are essential to realizing the translational potential of these innovative therapies. Clinical trials are underway to evaluate the safety, efficacy, and feasibility of nanotherapeutics for cancer treatment, indicating a clear path toward clinical translation.

Ethics approval and consent to participate

None.

CRediT authorship contribution statement

Jing Han: Writing – original draft, Validation, Conceptualization. **He Dong:** Writing – review & editing. **Tianyi Zhu:** Writing – review & editing. **Qi Wei:** Writing – review & editing. **Yongheng Wang:** Writing – review & editing. **Yun Wang:** Writing – review & editing, Conceptualization. **Yu Lv:** Writing – review & editing. **Haoran Mu:** Writing – review & editing. **Shandeng Huang:** Writing – review & editing. **Ke Zeng:** Writing – review & editing. **Jing Xu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jianxun Ding:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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