Advances in nanomedicine for cancer starvation therapy

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Abstract

Abnormal cell metabolism with vigorous nutrition consumption is one of the major physiological characteristics of cancers. As such, the strategy of cancer starvation therapy through blocking the blood supply, depleting glucose/oxygen and other critical nutrients of tumors has been widely studied to be an attractive way for cancer treatment. However, several undesirable properties of these agents, such as low targeting efficacy, undesired systemic side effects, elevated tumor hypoxia, induced drug resistance, and increased tumor metastasis risk, limit their future applications. The recent development of starving-nanotherapeutics combined with other therapeutic methods displayed the promising potential for overcoming the above drawbacks. This review highlights the recent advances of nanotherapeutic-based cancer starvation therapy and discusses the challenges and future prospects of these anticancer strategies.

Key words: drug delivery, nanomedicine, cancer starvation therapy, combination treatment

1. Introduction

Characterized by abnormal cell metabolism and growth with risk of metastasis, cancer remains a global fatal threat to human health today [1, 2]. In recent years, cancer starvation therapy is emerging as an effective method for suppressing tumor growth and survival through blocking blood flow or depriving their essential nutrients/oxygen supply [3-5]. The transport of nutrients could be blocked by stopping the tumor blood supply with the treatments of angiogenesis inhibiting agents (AIAs) [6, 7], vascular disrupting agents (VDAs) [8, 9] and transarterial chemoembolization (TACE) [10]. Moreover, agents that could consume the intratumoral nutrients/oxygen or mediate the essential substances uptake by tumor cells can also lead to tumor “starvation” and necrosis [4, 5, 11, 12]. Although some unique advantages have been exhibited for cancer treatment these years, concerns associated with these agents, such as low targeting efficiency, elevated tumor hypoxia, acute coronary syndromes, abnormal ventricular conduction, induced drug resistance and increased tumor metastasis risk, limit their further applications in clinic [13-16].

To overcome these challenges, combination therapy of cancer starvation agents with other cancer treating approaches has demonstrated to be an efficient way, which can maximize the therapeutic efficiency when compared to the single therapeutic method alone [17]. However, issues of the free drugs, such as undesirable drug absorption, poor bioavailability and rapid metabolism in vivo, have still been concerned [18]. The advances in micro-/nanotechnology as well as cancer biology have boosted development of drug delivery systems for cancer management with enhanced efficacy and limited side effects [19-22]. Among them, a variety of nanomaterials based on natural/synthetic polymers [23-29], liposomes [30], metal-organic frameworks (MOFs) [13], gold nanoparticles (NPs) [31] and silica NPs [11, 32, 33] have been employed to co-deliver cancer-starving agents and other therapeutics with...
the aim of reducing drug side effects [23], improving their targeting efficacy [26, 27], increasing the stability and half-life of therapeutics [13], and co-delivery of multiple drugs to overcome the drug resistance [34, 35]. Furthermore, cancer-starvation strategy associated with the multimodal nanomedicines have also been developed for achieving synergistic cancer therapy, which has been demonstrated to be the efficient way for overcoming the side effects of free drugs and resulting in superadditive therapeutic effects [14, 15, 20].

There are two major mechanisms in designing starving-nanotherapeutics. One is stopping/reducing the tumor blood supply through inhibiting/disrupting angiogenesis, or directly blocking the blood vessels [11, 23, 26, 36, 37]. The other is depriving essential nutrients/oxygen input of tumor cells through consuming the intratumoral nutrients/oxygen, or limiting the critical nutrients uptake [4, 38-40]. For maximizing the therapeutic efficiency, these therapeutics were cooperated with other cancer treating approaches, including chemotherapy [41, 42], gene therapy [43], phototherapy [44, 45], gas therapy [46], and immunotherapy [47]. Herein, we overview the recent efforts of leveraging nanomedicine-based drug delivery systems for cancer starvation therapy and focus on the major strategies of multimodal synergistic starvation treatments (Figure 1). Both the design principles and their anticancer performance of these formulations are highlighted. Finally, the challenges and future prospects of this field are discussed.

2. Nanomedicine-mediated cancer starvation therapy

2.1 Antiangiogenesis-related cancer starvation therapy

Tumor growth and metastasis highly depend on the angiogenesis, which is an essential step of neoplasms from benign to malignant transformation [48]. Anti-angiogenic therapy provides an efficient way for arresting the tumor growth through inhibiting the key angiogenic activators [7, 49]. Several AIAs have been approved by the Food and Drug Administration (FDA) for clinical cancer treatment since 2003 [7]. However, associated toxicities of these AIAs are nonnegligible according to the clinical/preclinical investigation, which includes hypertension, vascular contraction, regression of blood vessels and proteinuria [14, 17, 50].

2.1.1 Nano-antiangiogenesis-based cancer monotherapy

Compared to the free AIAs, nanomedicine could both improve their therapeutic outcomes via regulating their release behavior and increasing the drug accumulation in the tumor site through the enhanced permeability and retention (EPR) effect as well as actively targeting the tumor and/or endothelial cells via surface conjugation with target ligands [51, 52]. For example, mesoporous silica nanoparticles (MSNs) could significantly improve the targeting efficacy of tanshinone IIA (an angiogenesis inhibitor) to HIF-1α overexpression, leading to improved antiangiogenesis activity in a mouse colon tumor model (HT-29) [53]. Several over-expressed receptors, such as integrin αvβ3 and Neuropilin-1, were employed as the targets of nanomedicines, which showed enhanced targeting efficacy and improved tumor inhibiting rate [54-56]. Furthermore, paclitaxel (PTX) loaded antiangiogenic polyglutamic acid (PGA)-PTX-E-[c(RGDfK)2] nano-scaled conjugate could markedly suppressed the growth and proliferation of the αvβ3-expressing endothelial cells (ECs) and several cancer cells [57]. Additionally, bevacizumab, an angiogenesis inhibitor against vascular endothelial growth factor (VEGF) was directly used as a targeting ligand to modify magnetic iron oxide nanoparticles (IONPs), which was demonstrated to be an efficient platform for bevacizumab delivery in mice breast tumor (4T1) treatment [58].

Nanonization strategies for AIAs not only could reduce their associated toxicities and enhance the antitumor efficacy to some degree, but also provide a multidrug co-delivery platform toward enhancing the AIAs-based combination anticancer efficacy [31, 34,
2.1.2 Synergistic antiangiogenesis/chemotherapy

Angiogenesis inhibitors were often used together with chemotherapy for overcoming their shortages and enhancing the antitumor efficacy [17]. Recently, types of engineered anti-angiogenic nanotherapeutics have been developed for cancer combination treatment. For instance, doxorubicin (DOX) and mitomycin C (MMC) co-loaded polymer-lipid hybrid nanoparticles could significantly increase the animal survival and tumor cure rate compared with liposomal DOX for treating multidrug resistant human mammary tumor xenografts [34]. DOX combining with methotrexate (MTX), which was co-delivered by MSNs could also significantly improve the efficacy of oral squamous cell carcinoma treatment through down-regulating the expression of lymph dissemination factor (VEGF-C) [62]. Zhu and coworkers synthesized a matrix metalloproteinase-2 (MMP-2)-responsive nanocarrier for the co-delivery of camptothecin (CPT) and sorafenib, which was demonstrated to be an efficient approach for colorectal cancer synergistic therapy [63]. Curcumin (Cur), a potent antiangiogenesis agent, was co-loaded with DOX into pH-responsive poly(beta-amino ester) copolymer NPs for the 4T1 tumor treatment, which showed intensive anti-angiogenic and pro-apoptotic activities [64].

2.1.3 Synergistic antiangiogenesis/gene therapy

The co-delivery of antiangiogenesis drugs and gene silencing agents is considered to be another efficient way for cancer starvation therapy [43, 65-67]. For example, Lima and coworkers synthesized a chlorotoxin (CTX)-conjugated liposomes for anti-miR-21 oligonucleotides delivery, which promoted the efficiency of miR-21 silencing and enhanced the antitumor activity with less systemic immunogenicity [68]. Liu et al. also found that the fusion suicide gene (yCDglyTK) could induce tumor cell apoptosis more effectively after co-delivering with VEGF siRNA by a calcium phosphate nanoparticles (CPNPs), where the density of capillary vessels was also observed to obviously decrease in the xenograft tissue of gastric carcinoma (SGC7901) [67]. Furthermore, the poly-VEGF siRNA/thiolated-glycol chitosan nanocomplexes were employed to help overcome the resistant problem of bevacizumab by Kim and coworkers [65]. The results indicated that the combination of these two VEGF inhibitors produced synergistic effects with decreased VEGF expression and drug resistance.

2.1.4 Synergistic antiangiogenesis/phototherapy

Nanomaterial-based phototherapies that can selectively kill cancer cells without normal tissue injury have attracted extensive interest in the field of cancer treatments [69-71]. Enhanced antitumor efficacy was also observed when angiogenesis inhibitors and phototherapy agents were combined [31, 72]. For example, Kim and coworkers developed a hybrid RNAi-based AuNP nanoscale assembly (RNAi-AuNP) for combined antiangiogenesis gene therapy and photothermal ablation (Figure 2) [31]. AuNPs modified by single sense/anti-sense RNA strands could self-assemble into various geometrical nanoconstructs (RNAi-AuNP). Then, PEI/RNAi-AuNP complexes were prepared with branched polyethylenimine (BPEI) for the purpose of effective intracellular delivery. After intratumoral administration, the therapeutic effects of PEI/RNAi-AuNP complexes could be activated by continuous-wavelength lasers or high intensity focused ultrasound, which led to effective antiangiogenesis and tumor ablation. In another work, a carrier-free nanodrug was prepared by self-assembling of Sorafenib and chlorin e6 (Ce6) for antiangiogenesis and photodynamic therapy [72]. This nanodrug presented good passive targeting behavior in the tumor sites and effective reactive oxygen species (ROS) generation ability in vivo. The tumor inhibition rate was significantly improved after combination with Sorafenib. With additional merits, such as good biosafety and biocompatibility, this nano-integrated strategy promised potential for cancer synergetic treatment in clinic.

2.2 VDAs-based cancer starvation therapy

VDAs, as a unique class of anticancer compounds, is designed to selectively prevent the established abnormal tumor blood vasculature by targeting ECs and pericytes, leading to tumor starvation and central necrosis through hypoxia and nutrient deprivation [73]. However, they are powerless to the cancer cells at the tumor margin, which could draw oxygen and nutrients from the surrounding normal tissues [15]. Beside this, several other vascular risk factors, such as the acute coronary syndromes, blood pressure alteration, abnormal ventricular conduction, and transient flush, also limit the further application of free VDAs [73]. To overcome the above issues and enhance their antitumor ability, VDAs-based multimodal cancer therapies have been developed for solid tumor treatments [23, 27, 28, 42, 74-78].

2.2.1 Free VDAs-enhanced nanomedicine-based chemotherapy

The barriers of heterogeneity and high interstitial fluid pressure of solid tumors not only
limit the targeting efficiency of nanomedicines, but also weaken their antitumor ability against the tumor central area [79, 80]. Recent studies reported that small free molecule VDAs could help nanomedicines to overcome the above drawbacks [42, 74, 75]. For example, Chen and coworkers developed a coadministration strategy using free CA4P and CDDP-loaded PLC-g-mPEG NPs (CDDP-NPs) for complementing each other’s antitumor advantages and improving the antitumor efficiency [75]. The multispectral optoacoustic tomography (MSOT) images indicated that the tumor penetration of CDDP-NPs highly relied on the tumor vasculature, which aggregated in the peripheral region of the tumors. While co-administration of free CA4P and CDDP-NPs improved the tumor cellular killing efficiency both in the central and peripheral regions according to hematoxylin and eosin (H&E) staining. The enhanced antitumor efficiency against both murine colon cancer (C26) and human breast cancer (MDA-MB-435) models supported that this combination strategy was a promising way for solid tumor treatment.

Furthermore, small molecule VDAs could induce tumor target amplification of ligand-coated NPs through selectively modifying tumor vasculature. For example, protein p32, a stress-related protein which is specifically expressed on the surface of tumor cells [37], can selectively bind with the phage-displayed cyclic peptide (LyP-1) [81]. Ombrabulin, a small molecule VDAs, was used to induce the local upgraded presentation of protein p32 for enhancing the tumor “active targeting” of LyP-1 coated NPs. The in vivo results demonstrated that the recruitment of LyP-1 coated DOX-loaded NPs significantly increased after pretreating with ombrabulin when compared with the control groups [74]. In another work, coagulation-targeted polypeptide-based NPs were developed for improving their tumor-targeting accumulation by homing to VDA-induced artificial coagulation environment. The in vivo results showed that this cooperative targeting system recruited over 7-fold higher CDDP doses to the tumors than non-cooperative control groups [42]. The above cooperative targeting strategies combining with free VDAs and ligand-coated NPs showed obviously decreased tumor burden and prolonged mice survival compared to the non-cooperative controls.

![Figure 2](http://www.thno.org)
2.2.2 VDAs-nanomedicine induced synergistic starvation/chemotherapy

VDAs-nanomedicine could enhance their accumulation and retention at the leaky tumor vasculature via EPR effect, leading to high distribution and gradual release of VDAs around the immature tumor blood vessels as well as prolonged vascular disruption effect compared to free drugs [28]. Beside this, nanomedicine also provides a platform for VDAs-based cancer multimodal therapy [23, 27, 76, 78]. For instance, a multi-compartmental “nanocell” integrating a DOX-PLGA conjugate core and a phospholipid shell was prepared for achieving temporal release of DOX and combretastatin A4 (CA4) [23]. After accumulating at the tumor site, CA4 was released from the outer phospholipid shell of the nanocell rapidly and attacked the tumor blood vessels, and DOX was then released subsequently from the inner polymeric core for killing tumor cells directly. This mechanism-based strategy exhibited reduced side toxicity and enhanced therapeutic synergism in the progress of inhibiting murine melanoma (B16F10) and Lewis lung carcinoma growth.

Furthermore, several polymer-VDA conjugates caused amplified TME characteristics was also utilized to develop new cancer co-administration strategies [27, 78]. Hypoxia is one of the major features of solid tumors which can promote neovascularization, drug resistance, cell invasion and tumor metastasis [82, 83]. Meanwhile, the existence of hypoxia also provides the desired target for tumor selective therapy [21]. Tirapazamine (TPZ) is a typical hypoxia-activated prodrug (HAP), which own low toxicity toward normal tissues and can selectively kill the hypoxic cells after conversion into cytotoxic benzotriazinyl (BTZ) radical within hypoxic regions [84]. Nevertheless, the insufficient hypoxia level within tumors tremendously limited its further clinical application [85]. To address this, Chen and coworkers proposed a cooperative strategy based on VDA-nanomedicine and HAPs for solid tumor treatment (Figure 3) [27]. In this study, polyL-glutamic acid)-CA4 conjugate nanoparticles (CA4-NPs) were employed to selectively disrupt the abnormal vasculature of the tumor, as well as elevating the hypoxia level of the tumor microenvironment (TME). The intensive hypoxic TME further boosted the antitumor efficacy of TPZ subsequently. The in vivo results demonstrated that this combinational strategy can not only completely suppress the small tumor growth (initial tumor volume: 180 mm³), but also obviously keep down the size of large tumors (initial tumor volume: 500 mm³) without distal tumor metastasis. Moreover, Chen and coworkers also demonstrated that the expression of matrix metalloproteinase 9 (MMP9, a typical tumor-associated enzyme) in treated tumors (4T1) could be markedly increased by more than 5-fold after treatment with CA4-NPs. These overexpressed MMP9 could further activate the DOX release from a MMP9-sensitive doxorubicin prodrug (MMP9-DOX-NPs) and enhance the in vivo cooperative antitumor efficacy [78].

2.3 Vascular blockade-induced cancer starvation therapy

Besides the strategies of anti-angiogenic therapy and VDAs-induced tumor blood vessel disrupting, another promising strategy for cancer starvation therapy was proposed by shutting off the blood supply with nanothereapeutics that could selectively blockade tumor vascular and then inducing tumor necrosis.

2.3.1 Tumor-homing peptides-induced cancer starvation therapy

Tumor-homing peptides (THPs), such as pentapeptide (CREKA) and 9-amino acid cyclic peptide (CLT-1), could specially bind with fibrin-fibronectin complex in tumor blood clots [86]. Based on this, Ruoslahti and coworkers developed a CREKA modified IONPs for fibrin-fibronectin complexes targeting and subtle clotting in tumor vessels [87]. The initial deposition of these CREKA-IONPs created new binding sites for the subsequent NPs, and further enhanced the blood coagulation in the tumor lesion. The results indicated that the tumor imaging efficiency of this self-amplifying tumor homing system owned about six-fold enhancement compared to the control groups. However, the tumor inhibition efficiency of this system showed no significant improvement due to the insufficient tumor vessel occlusion. To this end, a cooperative theranostic system containing CREKA-IONPs and CRKDKC-coated iron oxide nanoworms was further developed by the same research group for improving the clots binding efficacy. The results proved that this combination system led to 60~ 70% tumor blood blockades and obvious tumor size reduction in vivo [88].

2.3.2 Thrombin-mediated cancer starvation therapy

Thrombin is a serine protease that catalyzes series of coagulation-related reactions and leads to rapid thrombus formation during the clotting process [48]. If thrombin can be precisely delivered to the tumor site and lead to selective occlusion of tumor-associated vessels by inducing the local blood
coagulation, it might be a promising way for inhibiting the growth and metastasis of tumors. Recently, a nucleolin-targeting multifunctional DNA nanorobotic system was constructed for smart drug delivery. The presence of the nucleolin subsequently triggered the opening of these DNA nanotubes and released the loaded therapeutic thrombin, which then led to specific intravascular thrombosis and tumor vessel blockade at the tumor site [26]. The growth of several tumor models was suppressed efficiently after treating with this thrombin-loaded DNA nanorobot, demonstrating that this system could become an attractive platform for cancer starvation therapy in a precise manner.

Figure 3. Schematic illustration of hypoxia-inducing VDA nanodrug combined with hypoxia-activated prodrug for cancer therapy (A). Tumor volume changes of BALB/c mice bearing 4T1 tumors with both moderate sizes (≈180 mm$^3$) (n=6), (B), and large sizes (≈500 mm$^3$) (n=6). (C). All data points are presented as mean ± standard deviation (s.d.). (*P<0.05, **P<0.01, ***P<0.001). Reproduced with permission from ref. [27]. Copyright 2019, Wiley-VCH.
2.3.3 Deoxygenation agent-induced cancer starvation therapy

It is known that insufficient oxygen (O\textsubscript{2}) supply could result in hypoxia-induced tumor cell necrosis [89]. Based on this, Zhang \textit{et al.} designed an injectable polyvinyl pyrrolidone (PVP)-modified magnesium silicide (Mg\textsubscript{2}Si) nanoparticle as a nano-deoxygenation agent (nano-DOA) for directly consuming the intratumoral O\textsubscript{2} and starving tumors [11]. This polymer-coated Mg\textsubscript{2}Si NPs could respond to the slightly acidic TME after the intratumoral injection, and be converted into silicon dioxide (SiO\textsubscript{2}) by scavenging the surrounding O\textsubscript{2} at the tumor site. As a byproduct, the \textit{in situ} formed SiO\textsubscript{2} aggregates further occluded the tumor capillaries and obstructed the follow-up nutrient and O\textsubscript{2} supply.

On the other hand, the intratumoral hypoxic level was also enhanced in the progress of O\textsubscript{2} consuming with the presence of DOA. Given this reason, Bu and coworkers prepared a TPZ loaded PVP-modified Mg\textsubscript{2}Si nanoparticles (TPZ-MNPs) for drug delivery and combination cancer therapy [38]. After intratumoral injection, the TPZ-MNPs quickly scavenged the O\textsubscript{2} \textit{in situ} and created an artificial anaerobic environment which caused the surrounding cell dormancy. Meanwhile, the released TPZ was activated in this promoted hypoxia TME, which further caused the now-dormant tumor cells death.

2.4 GO\textsubscript{x}-mediated cancer starvation therapy

Glucose is the major energy supplier for tumor growth and proliferation [90]. Glucose oxidase (GO\textsubscript{x}) can specifically catalyze the conversion of glucose into gluconic acid and hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) with the involvement of O\textsubscript{2}. This reaction can directly consume glucose and O\textsubscript{2}, and elevate the local acidity, hypoxia and oxidation stress \textit{in vivo}. Given this background, GO\textsubscript{x} has aroused considerable interest for cancer diagnosis and treatment in the past decade [4, 91]. Nevertheless, there are several limitations of this approach when using GO\textsubscript{x} as an anticancer agent. On the one hand, the overproduced H\textsubscript{2}O\textsubscript{2} of glucose oxidation can cause systemic toxicity and lethal chain reactions through directly damaging cell membranes, proteins and DNA of normal cells [92, 93]. On the other hand, similar glucose supply and physiological requirement of normal cells often lead to off-targeting and ineffective starvation treatment [94]. Through nanomedicine, GO\textsubscript{x} can co-delivery with other
therapeutic agents for cancer multimodal treatments [4]. Herein, we overview the recent representative GOx-based nanomedicines for cancer starvation therapy.

2.4.1 GOx-based cancer monotherapy

GOx could be used as an antitumor agent alone through consuming the intratumoral glucose and making the tumor “starving”. The continuously generated H2O2 could further lead to DNA damage and tumor cell apoptosis [95, 96]. For example, Dinda et al. prepared a GOx-entrapped biotinylated vesicle for active targeting cancer starvation therapy [97]. This GOx-containing system showed about six-fold higher tumor cell killing efficiency compared to normal cells through depleting the glucose supply for tumor cells in vitro. However, the glucose depletion efficiency was restrained by the hypoxic TME in vivo, because of the insufficient O2 supply in the solid tumor. Therefore, a hyaluronic acid (HA)-coated GOx and MnO2 coloaded nanosystem (GOx-MnO2@HA) was constructed for enhancing cancer starvation therapy outcome [98]. After uptaking by the CD44-expressing tumor cells, the local glucose was converted into gluconic acid and H2O2 with GOx catalysis. The generated H2O2 then reacted with MnO2 to generate O2, which further accelerated the local glucose-consumption. This nanosystem provided benefit to break the hypoxia obstacles and enhance the antitumor effect by GOx.

2.4.2 Synergistic starvation/chemotherapy

As discussed above, the concentration of generated H2O2 can be substantially elevated in the presence of GOx at the lesion site. The increased H2O2 level was exquisitely used to active the H2O2-sensitive prodrugs for enhancing the synergistic efficiency of both cancer starvation and chemotherapy [41, 99]. For example, Li et al. prepared a pH-responsive prodrug-based polymersome nanoreactor (GOx@PCPT-NR) that consisted of piperidine group, camptothecin (CPT) prodrug, PEG and GOx for cancer combination therapy (Figure 4) [41]. This polymersome nanoreactor owned prolonged blood circulation and high tumor accumulation efficiency. The terminal elimination half-life of GOx@PCPT-NR reached above 39 hours after intravenous injection. This drug delivery system also showed excellent stability and almost no H2O2 and free CPT were found within 48 h treatment in the plasma or liver. Nevertheless, the slight acidity of the tumor (pH = 6.8) could trigger the GOx release from the polymersome, which then catalyzed the conversion of intratumoral glucose into gluconic acid and H2O2. The enhanced acidity causing by the generated gluconic acid could further promote the GOx release, while the elevated H2O2 level could further accelerate the active CPT release. The accumulating effects amplified the combination antitumor efficiency [41]. Furthermore, this strategy was further confirmed by another biomimetic cascade nanoreactor (Mem@GOx@ZIF-8@BDOX) in vivo. As a byproduct of GOx-induced glucose depletion, gluconic acid could promote the release of loaded BDOX produrg from the nano-framework, and the released BDOX were then converted into DOX in the presence of elevated H2O2 at the tumor site [99].

2.4.3 GOx-inducing cancer starvation and hypoxia-activated chemotherapy

The consumption of molecular oxygen could increase the local hypoxia level in the progress of GOx-involved cancer therapy. This promoted hypoxic microenvironment was also employed to activate the hypoxia-activated prodrugs and amplify their antitumor activity [13, 30, 33, 100]. For example, a MOF-based biomimetic nanoreactor coating with erythrocyte membrane (eM) was developed for precise GOx and TPZ delivery and cancer combination therapy (Figure 5) [13]. The grafted biomimetic surface of the nanoreactor not only endowed it with prolonged blood circulation and immune-escaping property, but also enhanced the tumor homing efficiency of this nanosystem. After uptake by cells, the released GOx deprived the endogenous glucose and O2 which resulted in amplified hypoxic microenvironment and sufficient activation of TPZ. Based on the above synergistic cascade effects, a colon cancer model were efficiently inhibited in vivo. In another work, the PEG-modified long-circulating liposomes were used to sequentially deliver GOx and banoxantrone dihydrochloride (AQ4N, a hypoxia-activated prodrug) to tumors for cancer combination starvation/chemotherapy [30]. The in vivo photoacoustic image indicated that GOx-loaded liposome could obviously deplete the glucose of the tumor site, and lead to tumorous hypoxia enhancement. Under the elevated hypoxic microenvironment, the antitumor activity of the subsequent arrival liposome-AQ4N was activated by reducing low toxic AQ4N into high toxic 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydrox yanthrace-9,10-dione (AQ4) by the series of intracellular reductases. Synergistically enhanced antitumor effect was observed on 4T1 murine breast cancer model after treating with this liposome-based GOx/AQ4N co-delivery system. These results demonstrated that combination of GOx-based cancer starvation therapy and HAP-involved hypoxia-activated chemotherapy is an effective way for solid tumor treatment.
Furthermore, in order to reduce the systemic toxicity, Wang and coworkers developed a nanoclustered cascaded enzymes by crosslinking GOx and CAT with a pH-responsive block polymer poly(ethylene glycol)-block-poly(2-hydroxyethyl methacrylate) bearing 2-(2-carboxyethyl)-3-methylmaleic anhydride (PEG-b-PHEMA) with a BSA/BSATPZ (wt:wt, 1:2) outer shell for cancer starvation and hypoxia-activated chemotherapy [94]. The experimental data indicated that GOx and CAT could be released by the stimuli of the mild acidic TME after accumulating at the tumor site. Then, the release rate was self-accelerated by the subsequent generated gluconic acid with GOx-induced glucose consumption. Meanwhile, the aggravated hypoxia of TME further activated the BSATPZ which led to hypoxia-activated chemotherapy. Importantly, the authors also found that the present CAT could timely eliminate the appeared H2O2 as well as lowered the systemic toxicity of GOx-mediated cancer starvation therapy.

2.4.4 Starvation/oxidation synergistic therapy

Glutathione (GSH) is a natural antioxidant in the body, which prevents the damage of important cellular components by ROS, such as H2O2, hydroxyl radicals (•OH), and singlet oxygen (1O2). However, GSH could weaken the antitumor efficiency in the progress of ROS-mediated cancer therapy. To this end, Li et al. prepared GOx-loaded therapeutic vesicles based on a diblock copolymer containing a mPEG segment and copolymerized piperidine-functionalized methacrylate and phenylboronic ester (mPEG-b-P(PBEM-co-PEM)) [101]. After precise activation at the tumor site, the GOx-induced enzymatic reaction caused local consumption of glucose and O2 and generation of gluconic acid and H2O2. The generated H2O2 not only elevated the intracellular oxidative stress, but also led to the production of quinone methide (QM), which further suppressed the antioxidant ability of the tumor cells through depleting the intracellular GSH. These cumulative anticancer effects of the therapeutic vesicles resulted in effective cancer cell death and tumor ablation.

H2O2 can be transformed into the highly toxic ROS under certain conditions in vivo [71, 102]. For example, H2O2 could be disproportionated into •OH with the presence of Fenton reaction catalysts under acidic condition [103, 104]. While, in the presence of neutrophil-expressed phagocytic enzyme myeloperoxidase (MPO), H2O2 and chlorine ion (Cl−) could be converted into hypochlorous acid (HClO) through the enzymatic reaction [105]. Based on this, specific strategies were developed to combine with GOx for cancer starvation/oxidation synergistic therapy [106-110].

Figure 5. Schematic illustration of preparation of GOx and TPZ coloaded biomimetic nanoreactor with erythrocyte membrane coating (TGZ@eM) (A). TGZ@eM nanoreactor induced cancer starvation/hypoxia-activated chemotherapy (B). Reproduced with permission from ref. [13]. Copyright 2018, American Chemical Society.
In a recent study, Huo et al. designed a dendritic silica nanoparticle-based sequential nanocatalyst for co-delivering of GOx and Fe3O4 NPs (GOx-Fe3O4@DMSNs) for enhancing of combination anticancer efficiency (Figure 6) [106]. After EPR effect-induced accumulation of these nanocatalysts in the tumor site, the released GOx catalyzed the oxidation of the intratumoral glucose to gluconic acid and H2O2 and led to tumor starvation and central necrosis. Thereafter, the generated H2O2 sequentially were translated into highly toxic –OH by Fe3O4 NPs under the slightly acidic TME, which resulted in elevated oxidative stress and massive apoptosis of tumor cells. The final tumor inhibition rate of this nanomedicine by intravenous and intratumoral treatments with the same treating dose was reached to 64.7% and 68.9%, respectively. Besides this, another core-shell TME-responsive nanocatalyst, incorporated with a magnetic nanoparticle core of iron carbide (Fe5C2)-GOx and MnO2-nanoshell, was constructed by Lin and co-workers [107]. After endocytosis by tumor cells, the MnO2-nanoshell of this nanosystem was degraded into Mn2+ and O2 and resulted in GOx release under the stimuli of the acidic microenvironment. The generated O2 could enhance consumption of the local glucose with the presence of GOx, leading to sufficient tumor starving. Sequentially, the produced H2O2 further evolved into –OH catalyzed by Fe5C2, resulting in efficient tumor cell death. Recently, a smart autocatalytic Fenton nanosystem, consisted of GOx-loaded zeolitic imidazolate framework (ZIF) and adenosine triphosphate (ATP)-responsive metal polyphenol network (MPN) shell, was designed by Zhang et al. for the combination cancer therapy [108]. In tumor cells, the MPN shell was degraded into Fe3+ and tannic acid (TA) and further trigged the inner GOx release under the stimuli of the overexpressed ATP. Then, the exposed GOx led to endogenous glucose consumption and H2O2 accumulation. With the
Theranostics 2019, Vol. 9, Issue 26

presence of TA, the transition efficiency of Fe$^{3+}$ to Fe$^{2+}$ was accelerated, which further promoted the transformation of the generated H$_2$O$_2$ into high toxic \( \cdot \)OH by Fenton reaction. These accumulating antitumor effects significantly suppressed the tumor growth.

Silver (Ag) ions have been demonstrated to kill different types of cancer cells through increasing the intracellular oxidative stress, causing mitochondrial damage, and inducing cell autophagy [111, 112]. Based on this, Huang and coworkers designed a GOx-conjugated silver nanocube (AgNC-GOx) for efficient Ag ions delivery and synergistic starvation/metal-ion therapy [113]. AgNC-GOx catalyzed the glucose conversion into gluconic acid and H$_2$O$_2$ after uptake by the tumor cells. Cumulative gluconic acid elevated the acidity of TME which accelerated the AgNC degradation and Ag ions generation in the tumor site. Meanwhile, the generated H$_2$O$_2$ and Ag ions were found to lead the eradication of 4T1 cancer cells. Both the glucose consumption and accumulation of toxic H$_2$O$_2$ and Ag ions significantly suppressed the tumor growth and prolonged the mice survival.

HClO is a powerful ROS which can be generated by the MPO-mediated catalysis and owns higher cellular toxicity in comparison with H$_2$O$_2$. It has been proved to be a promising candidate for cancer therapy through disrupting some cellular functions and promoting the tumor cell death by the oxidation progress [114]. Given this pattern, Zhang and coworkers prepared an “artificial neutrophils”, consisting of GOx and chloroperoxidase (CPO) coloaded zeolitic imidazolate framework-8 (ZIF-8) core and neutrophil membrane (NM) coating (GOx-CPO@ZIF-8@NM), for both of cancer and infection treatments. NM coating help the NPs to target the tumor site efficiently (Figure 7) [109]. After uptake by the tumor cells, the embedded GOx and CPO were released from the ZIF-8 NPs, which synergistically enhanced the glucose depletion and HClO generation through a sequential enzymatic catalysis progress. According to the results, this artificial neutrophil can produced seven-fold higher reactive HClO than the natural neutrophils both in vitro and in vivo. Benefit from this, 4T1 tumors of mice was almost completely eradicated after treating with this neutrophil-mimicking NPs.

2.4.5 Synergistic starvation/phototherapy

Blue light irradiation (450~490 nm) could promote the Conversion of H$_2$O$_2$ into more toxic \( \cdot \)OH, which provides an alternative approach for cancer therapy. However, insufficient H$_2$O$_2$ supplies in the tumor site weaken the \( \cdot \)OH production as well as the antitumor efficiency. Instead, GOx, as an antitumor agent, could induce the glucose depletion and tumor starvation with consecutively generating of H$_2$O$_2$.

![Figure 7](http://www.thno.org)
Given this fact, Chang et al. developed GOx-conjugated polymer dots (Pdot-GOx) for enzyme-enhanced phototherapy (EEPT) [115]. After immobilizing into tumor, Pdot-GOx NPs could efficiently catalyze the glucose oxidation and steadily produce H₂O₂, which led to the enhancement of the local oxidative stress. Meanwhile, the appeared H₂O₂ could also be photolyzed to produce ·OH under light irradiation (460 nm) for killing tumor cells. The experimental results indicated that this EEPT strategy exhibited much higher efficacy in inhibiting MCF-7 tumor growth compared with the control groups in mouse models.

Photodynamic therapy (PDT) has proved to be a promising platform in imaging and treatment of cancers and other diseases [116]. As a noninvasive method, PDT utilizes the generated toxic ROS to destroy the cellular organelles and ablate tumors with the presence of photosensitizers under light irradiation. However, the poor penetration of the excitation light makes it powerless against deeply seated tumors [117]. Besides, hypoxia of TME is another suppressive factor for this O₂-dependent antitumor approach [118]. Thus, the combination with other strategies would be an alternative way for improving the efficiency of PDT-involved cancer therapy [119, 120]. Recently, Li et al. developed a GOx and catalase co-loaded porphyrin metal-organic framework with tumor cell membrane surface coating (mCGP) for synergistic starvation/PDT therapy. This mCGP NPs owned excellent tumor homing ability due to the tumor cell membrane surface coating. After internalized by tumor cells, the loaded catalase in mCGP was found to catalyze the generated H₂O₂ to disproportionate into molecular O₂ and H₂O, accelerating the consumption of endogenous glucose and promoting the production of ¹O₂ under light irradiation. These accumulating effects obviously enhanced the in vivo synergistic antitumor efficiency of mCGP NPs. In another work, Yu et al. developed a biomimetic nanoreactor (bioNR)-based starvation/PDT strategy for effective combating deeply seated metastatic tumors [32]. The bioNR was constructed based on a GOx and Ce6 conjugated hollow mesoporous silica NPs (HMSNs) with B16F10 cell membrane coating, which was filled with bis[2,4,5-trichloro-6-(pentyloxy carbonyl)phenyl]oxalate (CPPO) and perfluorohexane (PFC) in the cavity. After homing to the tumor, the peripheral glucose was converted into gluconic acid with H₂O₂. At the same time, the appeared H₂O₂ not only promoted the local oxidative stress of the tumor, but also could react with CPPO to generate chemical energy, which led to chemiluminescence resonance energy transfer-based PDT with the presence of Ce6. Furthermore, the molecular oxygen releases from PFC further increase the antitumor efficiency of O₂-dependent GOx-involved cancer starvation therapy and PDT. It was demonstrated that the Ce6-induced PDT effect for tumor metastasis was substantially enhanced after combination with GOx-involved cancer starvation therapy.

As described above, insufficient oxygen supply in solid tumors could limit the antitumor efficiency of GOx-related therapeutics. To address this challenge, Cai and coauthors prepared a HA-conjugated porous hollow Prussian Blue NPs (PHPBNs) for facilitating GOx delivery and tumor synergistic starvation/photothermal therapy [121]. The HA shell could enhance the targeting efficiency towards CD44 overexpressing tumors. After cellular endocytosis, the released GOx catalyzed the glucose depletion by consuming O₂ and PHPBNs sequentially catalyzed the generated H₂O₂ splitting into O₂ and H₂O to amplify the tumor starvation effect. Furthermore, GOx-induced glucose depletion not only inhibited the tumor growth, but also suppressed the expression of heat shock proteins (HSPs), where the latter facilitated PHPBNs-mediated low-temperature photothermal treatment to reduce their resistance. The results indicated that this combinational therapeutic system could significantly repress tumor growth in mice. In another work, Tang et al. developed a novel BSA-directed two-dimensional (2D) MnO₂ nanosheet (M-NS) by one-step method [122]. This M-NS not only owned an excellent GOx-like activity for catalyzing the local glucose oxidation, but also exhibited high photothermal conversion efficiency due to the large surface area. Furthermore, this M-NS artificial enzyme showed higher thermal stability than natural GOx. The experimental results indicated that the M-NS-induced intratumoral glucose depletion inhibited the ATP production as well as cellular HSPs expression, which promoted the sensitivity of tumors to the M-NS-mediated photothermal treatments.

### 2.4.6 Starvation/gas synergistic therapy

Previous studies have demonstrated that nitric oxide (NO) could be used as a therapeutic gas for cancer therapy through the nitroration of mitochondria and DNA or enhance the efficiency of PDT or radiation therapy[123, 124]. L-Arginine (L-Arg) is a natural NO donor which can release NO in the presence of inducible NO synthase enzyme (iNOS) or in the presence of H₂O₂ [125, 126]. Given this reality, Fan et al. employed a hollow mesoporous organosilica nanoparticle (HMON) for GOx and L-Arginine co-delivery (L-Arg-HMON-GOx) and cancer starvation/gas therapy (Figure 8) [46]. After accumulating at the tumor site, the intratumoral
glucose was transformed into gluconic acid and H$_2$O$_2$ by GOx. The generated H$_2$O$_2$ not only killed the tumor cells directly, but also enhanced the gas therapy effect through oxidizing L-Arginine into NO in the acidic TME. The in vivo experimental results indicated that L-Arg-HMON-GOx treated U87MG tumor bearing mice have the best tumor ablation outcome and much longer survival rate than the control groups, indicating the significantly promoted synergistic starvation/gas therapy effects.

2.4.7 GOx-mediated starvation/immunotherapy

Although cancer immune checkpoint blockade (ICB) therapy has been witnessed exciting progress in treating many types of cancers in clinic, several remaining challenges still need to be overcome in ICB-related cancer immunotherapy, such as low immune response efficacy, off-target side effects, and immune suppressive factors in TME [127-131]. Combination of cancer immunotherapy with other anticancer methods has been considered as an efficient strategy for addressing these issues [132-138]. For example, Xie et al. presented a therapeutic method combing with cancer cell membrane coated GOx-loaded mesoporous silica nanoparticles (CMSN-GOx) and anti-programmed cell death protein 1 (anti-PD-1) for cancer starvation/immunotherapy (Figure 9) [47]. Contributing to the CM coating, CMSN-GOx was efficiently delivered to the tumor site. The released GOx could not only catalyze the glucose depletion to inhibit the tumor growth, but also induce more dendritic cells (DCs) maturation which further enhanced the antitumor efficacy of anti-PD-1. In vivo experimental results indicated that CMSN-GOx plus anti-PD-1 combination treatment provided more effective tumor suppression than any single therapies.

2.4.8 GOx-involved multimodal synergistic therapy

As previously reported, H$_2$O$_2$ generated in the GOx-induced glucose oxidation could split into high toxic ∙OH radicals through Fenton reaction in the presence of Fe$_3$O$_4$[106]. The rising tumor temperature could further elevate the conversion efficiency of local H$_2$O$_2$ to ∙OH as well as enhance the antitumor ablation [71]. Given this fact, Feng et al. developed a Fe$_3$O$_4$/GOx co-loaded polypyrrole (PPy)-based composite nanocatalyst (Fe$_3$O$_4$@PPy@GOx NC) for multimodal cancer therapy. Fe$_3$O$_4$@PPy@GOx NCs could selectively accumulate at the tumor site (4T1) via EPR effect. Thereafter, the released GOx-mediated intratumoral glucose oxidation elevated the H$_2$O$_2$ level and acidity of TME, which sequentially resulted in local ∙OH accumulation and tumor cell death. At the same time, the polypyrrole (PPy) component which owned a high photothermal-conversion efficiency (66.4% in NIR-II biowindow) considerably increased the tumor temperature in both in NIR-I and NIR-II biowindows, which accelerated the H$_2$O$_2$ disproportionation as well as enhanced the photothermal-enhanced cancer starvation/oxidation therapy.
2.5 Other strategies for cancer starvation therapy

Recently, types of special strategies in this field, which aimed at some critical nutrients, such as lactate and cholesterol, were also developed [39, 40, 139-141].

Lactate, which was once considered to be the waste product of glycolysis, has been demonstrated that can “fuel” the oxidative tumor cells growth as an energy substrate [12, 142]. Investigation indicated that interfering the lactate-fueled respiration could selectively kill the hypoxic tumor cells \(\text{via} \) inhibiting the expression of lactate-proton symporter, monocarboxylate transporter 1 (MCT1) [143]. Meanwhile, the reduction of lactate uptake by inhibiting the expression of MCT1 could transform the lactate-fueled aerobic respiration to anaerobic glycolysis as well as lower the \(\text{O}_2\) consumption in tumor cells which would facilitate the \(\text{O}_2\)-depleting cancer therapy. For example, Zhang and coworkers developed an \(\alpha\)-cyano-4-hydroxycinnamate (CHC) loaded porous Zr (IV)-based porphyrinic metal-organic framework (PZM) NPs with HA coating for cancer combination therapy (Figure 10) [40]. After effectively accumulating at the CT26 tumors, the released CHC could obviously decrease the expression of MCT1 and turn down the lactate uptake which leading to lower the \(\text{O}_2\) consumption. As a result, the PDT efficiency was markedly enhanced due to the sufficient \(\text{O}_2\) converting upon the laser irradiation (600 nm). Additionally, reducing the production of lactate \(\text{via} \) knockdown of lactate dehydrogenase A (LDHA) in tumor cells was also demonstrated that could neutralize of the tumor acidity and enhance the anti-PD-L1-mediated immunotherapy [139].

Recently, Thaxton and coworkers designed synthetic high density lipoprotein nanoparticles...
(HDL-NPs) with gold NPs as a size- and shape-restrictive template for lymphoma starvation therapy [39]. This HDL-NPs could especially target scavenger receptor type B-1 (SR-B1), which is a high-affinity HDL receptor expressed by lymphoma cells. This combination of SR-B1 promoted the cellular cholesterol efflux and limited the cholesterol delivery, which selectively induced cholesterol starvation and cell apoptosis. The B-cell lymphoma growth was obviously inhibited after HDL-NPs treatment of B-cell lymphoma bearing mice. Furthermore, this HDL-NPs could reduce the activity of myeloid-derived suppressor cells (MDSCs), a type of innate immune cells that potently inhibit T cells, through specifically binding with SR-B1 of MDSCs [140]. In Lewis lung carcinoma mice model, the in vivo data showed that the suppression of MDSCs by HDL-NPs markedly increased CD8+ T cells and reduced Treg cells in the metastatic TME. After treating with HDL-NPs, the tumor growth and metastatic tumor burden were obviously reduced and the survival rate was clearly improved due to enhanced adaptive immunity.

3. Conclusion and outlook

As an attractive strategy for cancer treatment, nanomedicine-mediated cancer starvation therapy could selectively deprive the nutrients and oxygen supply through antiangiogenesis treatment, tumor vascular disrupting or blockade, direct depletion of the intratumoral glucose and oxygen, and other processes. Moreover, by combining with chemotherapeutic drugs, therapeutic genes, enzymes, metal NPs, hypoxia-activated prodrugs, inorganic NPs, Fenton-reaction catalysts, photosensitizers, or photothermal agents, two or more therapeutic agents could be readily integrated into one single formulation, leading to enhanced treatment outcomes (Table 1).

Figure 10. Schematic illustration of porphyrinic MOF nanoplatform mediated suppressing lactate-fueled respiration for enhanced PDT therapy (A). Tumor volume changes (n=5). (B) and body weight curves (n=5). (C). Of CT26 tumor bearing mice after different treatments. All data points are presented as mean ± standard deviation (s.d.). (**P<0.001). Reproduced with permission from ref. [40]. Copyright 2018, Wiley-VCH.
| Strategies | Materials | Therapeutics | Administration route | Treatments | Tumor models | Ref. |
|------------|-----------|--------------|----------------------|------------|--------------|-----|
| Antiangiogenesis-related cancer starvation therapy | αβ3-integrin targeted perfluorocarbon NPs | Docetaxel-prodrug | i.v. injection | Antiangiogenesis therapy | Vx2 tumor bearing rabbits | [54] |
| | Chitosan NPs | Ursolic acid | Oral administration | Antiangiogenesis therapy | H22 tumor bearing mice | [145] |
| | PCA-PTX-E-[c(RGDfK)2] | PTX | i.v. injection | Antiangiogenesis therapy | 4T1 tumor bearing mice | [57] |
| Recombinant human endostatin conjugated AuNPs | Recombinant human endostatin | Subcutaneous injection | Antiangiogenesis therapy | SW620 tumor bearing mice | [146] |
| MSNs | Tanshinone IIA | i.v. injection | Antiangiogenesis therapy | HT-29 tumor bearing mice | [53] |
| MAMSNs-PET-PET-KALA NPs | anti-VEGF siRNA | i.v. injection | Antiangiogenic gene therapy | A549 tumor bearing mice | [43] |
| | Free CA4 and DOX | i.v. injection | Dual antiangiogenic therapy | Vx2 tumor bearing rabbits | [55] |
| | Free CA4 and DOX | i.v. injection | Dual antiangiogenic therapy | A431 tumor bearing mice | [65] |
| Thiolated-glycol chitosan formed NPs | DOX and MMC | i.v. injection | Antiangiogenesis therapy and chemotherapy | MDA-MB 435/LCC6/WT tumor bearing mice and MDA-MB 435/LCC6/MDR1 tumor bearing mice | [64] |
| Polymer-lipid hybrid NPs | DOX and MTX | i.v. or oral administration | Antiangiogenesis therapy and chemotherapy | Oat SCC tumor bearing mice | [62] |
| pH and thermo-responsive MSNs | AXT and CST | i.v. injection | Antiangiogenesis therapy and chemotherapy | SCC7 tumor bearing mice | [147] |
| | Fumagillin prodrug and zoledronic acid | i.v. injection every | Antiangiogenesis therapy and chemotherapy | HT-29 tumor bearing mice | [63] |
| | Bevacizumab and poly-anti-VEGF siRNA | i.v. oral administration | Antiangiogenesis therapy and gene therapy | GBM tumor bearing mice | [68] |
| | DOX and Cur | i.v. injection | Antiangiogenesis therapy and chemotherapy | SMMC 7721 tumor bearing mice | [64] |
| | Captopril-polylethenylene mine conjugated AuNPs | Captopril and siRNA | i.v. injection | Antiangiogenesis and gene therapy | MDA-MB-435 tumor bearing mice | [66] |
| | Calcium phosphate NPs | anti-VEGF shRNA and yCDglyTK | Intraperitoneal or intratumoral administration | Antiangiogenic gene therapy and suicide gene therapy | SOC/2901 tumor bearing mice | [67] |
| | CTX and anti-miR-21 | i.v. oral administration | Antiangiogenesis therapy and gene therapy | GBM tumor bearing mice | [68] |
| DOX-PLGA-conjugate NPs | Rhoj antibody | i.v. injection | Antiangiogenesis therapy and radiotherapy | Patient-derived tumor xenografts | [61] |
| | Anti-VEGF siRNA | Intratumoral injection and laser irradiation (655 nm) | Antiangiogenic gene therapy and photothermal therapy | PC-3 tumor bearing mice | [31] |
| Near infrared probe iron oxide NPs | Bevacizumab | i.v. injection | Antiangiogenesis and imaging | 4T1 tumor bearing mice | [58] |
| | Sorafenib and Ce6 | i.v. injection and laser irradiation (660 nm) | Antiangiogenesis therapy and photodynamic therapy | HSC3 tumor bearing mice | [72] |
| VDAs-based cancer starvation therapy | DOX-PLGA-conjugate NPs | Free CA4 and DOX | i.v. injection | Starvation therapy and chemotherapy | Lewis lung carcinoma xenografts and B16F10 tumor bearing mice | [23] |
| | LyP-1 coated liposomes | Free Ombrabulin and DOX | i.v. injection | Starvation therapy and chemotherapy | MDA-MB-435 tumor bearing mice | [74] |
| | Poly(L-glutamic acid)-g-mPEG NPs | Free CA4P and CDDP | i.v. injection | Starvation therapy and chemotherapy | MDA-MB-435 tumor bearing mice | [75] |
| | A15-PEG-CDDP NPs | Free DMXAA and CDDP | i.v. injection | Starvation therapy and chemotherapy | C26 tumor bearing mice | [42] |
| | CA4-NPs | CA4 | i.v. injection | Starvation therapy | C26 tumor bearing mice | [28] |
| | mPEG-b-PHEA-DMXAA conjugate NPs | DMXAA and DOX | i.v. injection | Starvation therapy and chemotherapy | MCF-7 tumor bearing mice | [76] |
| | CA4-NPs | CA4 and TPZ | i.v. injection | Starvation therapy and chemotherapy | 4T1 tumor bearing mice | [27] |
| | 2MECA modified iONPs and CRKDKC modified iron oxide nanoworms DNA nanorobots | Two tumor-homing peptide of 2MECA and CRKDKC | i.v. injection | Starvation therapy and chemotherapy | 4T1 and C26 tumor bearing mice | [78] |
| | PVP-modified MgSi NPs | MgSi | Intratumoral injection | Starvation therapy | 22R1 tumor bearing mice | [88] |
| | TFZ-MNP | MgSi and TPZ | Intratumoral injection | Starvation therapy and hypoxia-activated chemotherapy | 4T1 tumor bearing mice | [58] |
However, most innovations in this field are still in their infancy, with underlying challenges regarding clinical translation that need to be assessed in detail. For example, the biosafety of these nanomaterials is still significantly concerned, especially for the non-biodegradable formulations. Although the
biosafety assessment of these materials could be systematically evaluated through animal models, long-term internal metabolic behaviors and related toxicity should be thoroughly investigated before clinical application. Another major concern is the aggravating hypoxia level that may accelerate the tumor invasion and metastasis in the progress of tumor starvation therapy. Detailed studies should be performed to confirm whether cancer starvation therapy could turn on the tumor metastasis switch by elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to therapy could turn on the tumor metastasis switch by elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects. Moreover, in addition to elevating the hypoxic TME, which would also help to develop new combination strategies for offering synergistic effects.

4. Abbreviations

Table 2. List of abbreviations

| Abbreviation | Description |
|--------------|-------------|
| OH           | Hydroxyl radical |
| O2           | Singlet oxygen |
| 2D           | Two-dimensional |
| AIA          | Angiogenesis inhibiting agent |
| anti-PD-1    | Programmed cell death protein 1 antibody |
| anti-PD-L1   | Programmed cell death ligand 1 antibody |
| A431         | Human epidermoid carcinoma cell line |
| A449         | Human lung cancer cell line |
| Ag           | Silver |
| ATP          | Adenosine triphosphate |
| Au NP        | Gold nanoparticle |
| B16F10       | Mouse melanoma cell line |
| BDOX         | H2O2-sensitive doxorubicin prodrug |
| BPEI         | Branched polyethyleneimine |
| BSA          | Bovine serum albumin |
| BCE          | PEG-l-PHEMA crosslinked CPZ loaded BSA and CAT/GOx nanoclustered enzymes |
| C26          | Murine colon cancer cell line |
| C8161        | Human melanoma cell line |
| CT26         | Mouse colon cancer cell line |
| CA4          | Combretastatin A4 |
| CA4P         | Combretastatin A4 disodium phosphate |
| CA4-NPs      | Poly(L-glutamic acid)-CA4 conjugate nanoparticles |
| CDDP         | Cisplatin |
| Ce6          | Chlorin e6 |
| CHC          | a-cyano-4-hydroxycinnamate |
| CM           | Cell membrane |
| CMSNs        | Cancer cell membrane coated mesoporous silica nanoparticles |
| CPN          | Calcium phosphate nanoparticles |
| CPO          | Chloroperoxidase |
| CPPO         | Bis[2,4,5-trichloro-6-(pentyloscarybonyl)phenyl]oxalate |
| CST          | Camptothecin |
| CTX          | Chlorotoxin |
| Cur          | Curcumin |
| DDS          | Drug delivery system |
| DCs          | Dendritic cells |
| DOX          | Doxorubicin |
| ECs          | Endothelial cells |
| EEPT         | Enzyme-enhanced phototherapy |
| eM           | Erythrocyte membrane |
| EMT-6        | Mouse mammary cancer cell line |
| EPR          | Enhanced permeability and retention |
| FDA          | Food and Drug Administration |
| FDMSNs       | Ferrocene-functionalized dendritic mesoporous silica nanoparticles |
| GBI          | Human glioblastoma cell line |
| GO           | Graphene oxide |
| GOG          | Glucose oxidase |
| GSH          | Glutathione |
| H2O2         | Hydrogen peroxide |
| HA           | Hyaluronic acid |
| HAP          | Hypoxia-activated prodrug |
| HDL          | High density lipoprotein |
| HFR          | Heparin-folic acid-retinoic acid conjugate |
| HMON         | Hollow mesoporous organosilica nanoparticle |
| H22          | Mouse hepatocellular carcinoma cell line |
| HepG2        | Human liver cancer cell line |
| HSC3         | Human oral squamous carcinoma cell line |
| HSP          | Heat shock protein |
| HT-29        | Mouse colon tumor cell line |
| IC9          | Indocyanine green |
| ICB          | Immune checkpoint blockade |
| inNGR-NP     | InNGR-modified PEG-PLGA nanoparticle |
| inOS         | NO synthase enzyme |
| iONP         | Iron oxide nanoparticle |
| i.v.         | Intravenous injection |
| LyP-1        | Phage-displayed cyclic peptide |
| LLC          | Lewis lung carcinoma cell line |
| MCF-7        | Human breast cancer cell line |
| MCT1         | Monocarboxylate transporter 1 |
| MDA-MB-435   | Human breast cancer cell line |
| MDA-MB-231   | Human breast cancer cell line |
| MDR          | Multidrug resistance |
| MDSCs        | Myeloid-derived suppressor cells |
| MgSi         | Magnesium silicide |
| MGP          | GOx and MnCO coloaded poly(lactic-co-glycolic acid) nanoparticles |
| MIL-100      | Ferric ions contained metal organic framework |
| MGH          | GOx loaded MIL-100 with polydopamine-modified hyaluronic acid coating |
| MMC          | Mitomycin C |
| MMP          | Matrix metalloproteinase |
| MnO2         | Manganese dioxide |
| M-NS         | BSA-directed two-dimensional MnO2 nanosheet |
| MOF          | Metal-organic framework |
| MOST         | Multispectral optoacoustic tomography |
| MPN          | Metal polyphenol network |
| MSN          | Mesoporous silica nanoparticle |
| MTX          | Methotrexate |
| nano-DAS     | Nano-deoxygenation agent |
| NC           | Nanocatalyst |
| NIR          | Near-infrared |
| NM           | Neutrophil membrane |
| NO           | Nitric oxide |
| NP           | Nanoparticle |
| NR           | Nanoractor |
| O2           | Oxygen |
| OCI          | Hypochlorite ion |
| OSCC         | Oral squamous carcinoma cell line |
| PC-3         | Human prostate cancer cell line |
| Pdot         | Polymer dot |
| PDT          | Photodynamic therapy |
| PFC          | Perfluorocarbon |
| PLA          | Poly-L-arginine |
| PLL          | poly (L-lysine) |
| PLGA         | Poly(lactic-co-glycolic acid) |
| PEG          | Poly(ethylene glycol) |
| PEG-4-PHEMA   | poly(ethylene glycol)-block-poly(2-hydroxyethyl methacrylate) |
| PLG-4-mPEG   | Poly(L-glutamic acid)-g-methoxy poly(ethylene glycol) |

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Competing Interests
The authors have declared that no competing interest exists.

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