Review Article

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Recent process of using nanoparticles in the T cell-based immunometabolic therapy

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Abstract: Immunotherapy is currently the main treatment for malignant tumors by activating immune cell. Metabolic reprogramming in tumor microenvironment can greatly affect the function of immune cell, and T cell is the main anti-tumor effector cell. Therefore, the T cell-based immunometabolic therapy can improve clinical efficacy. In T cell-based immunometabolic therapy, regular agents in conventional forms are difficult to achieve the intended efficacy due to poor tumor permeability and low cellular uptake. Nanoparticle-based strategy can serve as the optimal targeted drug delivery system due to co-encapsulation of multiple therapeutic agents and stable loading. Here, we intend to summarize examples of nanoparticles in the T cell-based immunometabolic therapy, and provide a comprehensive and helpful review by covering notable and vital applications of nanotechnology-based strategies for T cell-based immunometabolic therapy.

Keywords: nanoparticles, immunotherapy, T cell, immunometabolism

Abbreviations

ACT	adoptive T-cell therapy
Akt	protein kinase B
ANs	AP-based nanoparticles
AP	amphiphilic poly (γ-glutamic acid)
CA	cis-aconitate
CAR	chimeric antigen receptor
CD	cluster of differentiation
Ce6	Chlorin e6
CRISPR	clustered regularly interspaced short palindromic repeats
DEAP	3-diethylamino propyl isothiocyanate
DHCR7	7-dehydrocholesterol reductase
DPPA-1	d-peptide antagonist of programmed cell death-ligand 1
F/ANs	fenofibrate-loaded fANs
fAP	fluorescent dye-labeled AP
fANs	fAP-based nanoparticles
FDA	Food and Drug Administration
FOXM1	Forkhead box M1
GA	glycolic acid
HRR	homologous recombination repair
ICI	immune checkpoint inhibitors
IDO1	indoleamine 2,3-dioxygenase 1
LA	lactic acid
MMP-2	matrix metalloproteinase-2
MPS	metabolic pathway subtype
mTOR	mammalian target of rapamycin
PAP	prostatic acid phosphatase
PBAE	poly β-amino ester
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PDT	photodynamic therapy
PI3K	phosphoinositide 3-kinase
PLGA	poly lactic-co-glycolic acid
PLL	ε-poly-L-lysine
PPAR	peroxisome proliferator-activated receptor
PS	photosensitizers
ROS	reactive oxygen species
TCR	T cell receptor
TK	thioketal
TME	tumor microenvironment
TNBC	triple-negative breast cancer

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1 Introduction

Cancer is a serious threat to public health [1]. There were an estimated 19.3 million new cancer cases and 10.0 million cancer deaths in 2020. In addition to traditional treatment methods such as surgery, radiotherapy, and chemotherapy, immunotherapy is a rapidly developing new generation of tumor therapy, which has great clinical application prospects [2]. Immunotherapy, mainly including immune checkpoint inhibitors (ICI), adoptive T-cell therapy (ACT), tumor vaccines, and nonspecific immunomodulators, can activate the immune system and eliminate cancer [2–4]. In 2010, the first tumor vaccine (sipuleucel-T) for prostate was approved by the Food and Drug Administration (FDA), which can activate the anti-prostatic acid phosphatase (PAP) immune response [5]. In 2011, the FDA approved the first cytotoxic T lymphocyte-associated antigen-4 monoclonal antibody, ipilimumab, based on the phase III trial (MDX010-20) for metastatic melanoma patients [6,7]. In 2017, the FDA approved the chimeric antigen receptor (CAR) T cell therapy, Yescarta (axicabtagene ciloleucel, cluster of differentiation (CD) 19 CAR T cell) and Kymriah (tisagenlecleucel, CD19 CAR T cell), for the treatment of hematological malignancies [8]. With rapid development, immunotherapy has played an equal role in surgery, chemoradiotherapy, and targeted therapy in tumor treatment, but it still faces challenges [9,10]. In advanced cancer patients, only around 10–40% respond to programmed cell death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) monotherapy, and others are primarily resistant [11]. In melanoma patients sensitive to anti-PD-1/PD-1 monoclonal antibody, nearly 60% would develop acquired resistance [12]. In addition, undesired side effects associated with systemic dissemination are also observed in patients receiving immunotherapy [13–15].

As is known, metabolic reprogramming of the tumor microenvironment (TME) greatly affects the anti-tumor ability of immune cell, which is a key factor affecting the efficacy of immunotherapy (Figure 1) [16–19]. In TME, tumor cell frantically obtains oxygen and nutrients (including glucose, fatty acids, glutamine, *etc.*) to meet their metabolic needs, and the deficiency of energy sources leads to the suppression of immune cell metabolism [20]. In turn, metabolites, including lactic acid, reactive oxygen species (ROS), and adenosine, can work as immunosuppressive factors [21–26]. Platten *et al.* found that tumor cell can highly express indoleamine 2,3-dioxygenase 1 (IDO1) to catabolize tryptophan to kynurenine, and this could limit the tryptophan supply to T cell, thereby inhibiting the proliferation and function of T cell [27]. Kynurenine can also activate aromatic hydrocarbon receptors, which results in immunosuppression [28–30]. Several small molecule inhibitors targeting IDO1 have entered clinical trials, but whether IDO1 inhibitors will bring clinical utility remains unclear [31]. Therefore, an imminent challenge for T cell-based immunometabolic therapy is to develop effective strategies to realize the potential for clinical application [32–36].

However, the complexity of the TME has been found to increase difficulty of developing T cell-based immunometabolic therapy [37]. Lack of selectivity for tumor cells lead to inefficient drug delivery in T cell-based immunometabolic therapy, which limit clinical application [37]. In addition, nontumor-specific immune activation led to systemic side effects [37]. To implement T cell-based immunometabolic therapy, nanoparticles can work as the scientific and

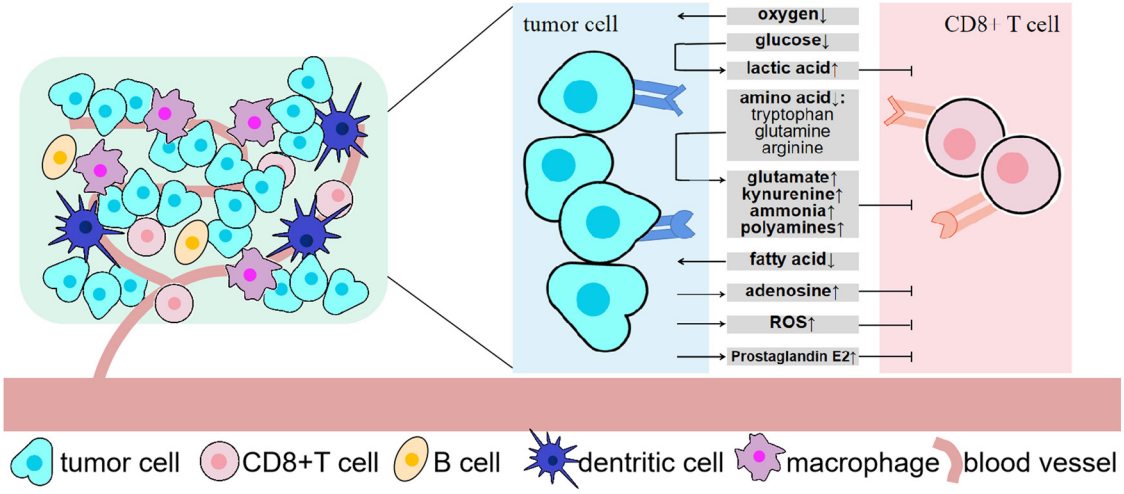

Figure 1: Metabolic competition between tumor cell and $CD8^+$ T cell. In the TME, tumor cell takes up a large amount of metabolic raw materials and accumulate metabolic wastes, leading to metabolic disorders of $CD8^+$ T cell.

practical drug delivery systems based on their biocompatibility and ability to improve drug circulation and targeting [38,39]. Herein, we systematically introduce these immunotherapies, and focus on various applications of nanoparticles in T cell-based immunometabolic therapy.

2 Application and development of nanoparticles

Nanoparticles can be divided into organic nanoparticles (including lipid nanoparticles, polymer nanoparticles, *etc.*) and inorganic nanoparticles (including metal nanoparticles, inorganic non-metallic nanomaterials, *etc.*), and exhibit many advantages in drug delivery, including stable loading, specific delivery, improved bioavailability, and co-encapsulation of multiple therapeutic agents [38,39]. Since the first nanomedicine was approved by the FDA in 1995, several nanomedicines have been applied in cancer treatment [40–43]. As immunotherapy plays an increasingly important role in tumor treatment, nanotechnology has emerged as an attractive and effective strategy to enhance anti-tumor immune response [44].

2.1 Nanoparticles that modulate T-cell metabolism

As is known, there exists intense nutritional competition between tumor cell and immune cell [20–24]. In TME, *naive* T cell mainly depends on oxidative phosphorylation, but upon activation, T cell switches metabolism into aerobic glycolysis *via* the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway to support the differentiation into effector T cell [45–48]. To upregulate the anti-tumor activity of T cell, metabolism-modulating drugs can be applied to inhibit tumor cell metabolism or promote T cell nutrient uptake [16,17]. Nanoparticles can work as the optimal targeted drug delivery system of metabolism-modulating drugs [40,41].

Kim *et al.* reported an application of nanoparticle-mediated lipid metabolic reprogramming in T cell [49]. Based on carbodiimide crosslinking reaction, grafting phenylalanine ethyl ester with poly (γ-glutamic acid) synthesized amphiphilic poly (γ-glutamic acid) (AP). Fenofibrate was packaged in AP-based nanoparticles (ANs) or fluorescent dye-labeled AP-based nanoparticles (fANs), and then fenofibrate-loaded fANs (F/ANs) were obtained. The surface of F/ANs was modified with anti-CD3ef(ab')2 fragment to yield aCD3/F/ANs and achieve targeted delivery of T cell (Figure 2a and b). Fenofibrate can up-regulate expression levels of peroxisome proliferator-activated receptor (PPAR)-α and fatty acid translocase CD36. After treating with aCD3/F/ANs, the expression of PPARα and CD36 on cell membrane was increased in T cell. This resulted in a 3.1-fold increase in lipid uptake by T cell treated with aCD3/F/ANs, thus affecting the survival and proliferation of T cell (Figure 2c and d). Treatment with aCD3/F/ANs significantly enhanced the $CD8^+$ T cell, as well as secretion of IFN-γ and granzyme B. The anti-cancer effect of T cell is limited, mainly because of glucose deficiency in TME. In this work, aCD3/F/AN can reprogram the mitochondrial lipid metabolism of T cell in glucose deficiency in TME with low glucose, and enhance the survival and effect function of T cell. These results provided strong evidence that nanoparticle-based drug delivery systems displayed great potential in the T cell-based immunometabolic therapy.

2.2 Nanoparticles that combine T-cell metabolism and ICIs

ICIs can restore effective T cell function by blocking the immune checkpoints, and are widely used in tumor treatment [50,51]. According to the metabolic characteristics, Gong *et al.* divided triple-negative breast cancer (TNBC) into three heterogeneous metabolic pathway subtype (MPS), and anti-LDH therapy can enhance tumor response to anti-PD-1 monoclonal antibody in MPS2 (the glycolytic subtype with upregulated carbohydrate and nucleotide metabolism) [52]. Therefore, the metabolic reprogramming in TME significantly affects the efficacy of ICIs. However, the optimal T cell-based immunometabolic therapy to undergo treatment at low doses and reduce related adverse events remains to be explored.

Facing these challenges, Cheng *et al.* reported a therapeutic peptide assembling nanoparticle for dual-targeted cancer immunotherapy, namely NLG919@DEAP-^{D}PPA-1-Scr [53], which contain amphiphilic peptide and the IDO1 inhibitor (NLG919). The amphiphilic peptide was designed to consist of a functional 3-diethylamino propyl isothiocyanate (DEAP) molecule, a peptide substrate of matrix metalloproteinase-2 (MMP-2), and a short d-peptide antagonist of programmed cell death-ligand 1 (^{D}PPA-1) (Figure 3a). When in the weakly acidic environment, protonated DEAP and cleavage by MMP-2 result in the local release of ^{D}PPA-1 and NLG919 in tumor region. In the tumor-bearing mice, this sequentially responsive therapeutic peptide assembling nanoparticles can simultaneously block immune checkpoints and tryptophan metabolism, thereby promoting the activation of cytotoxic T lymphocytes, slowing melanoma growth and

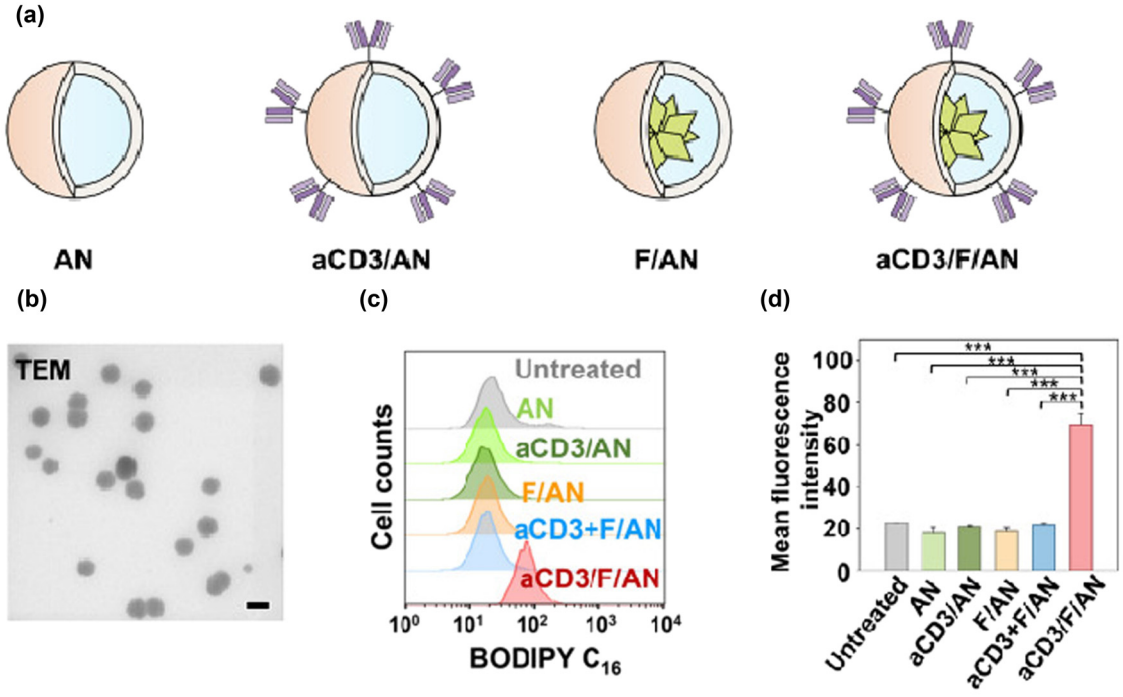

Figure 2: Application of nanoparticle-mediated lipid metabolic reprogramming in T cell. (a) Schematic illustration of the nanoparticle. (b) Morphology of aCD3/F/ANs. Scale bar: 200 nm. After treatment in different groups, the association of fluorescent lipid with T cell was determined by flow cytometry (c) and expressed as mean fluorescence intensity (d) (***$P < 0.001$). Reproduced from Ref. [49]. Copyright 2021, Springer Nature.

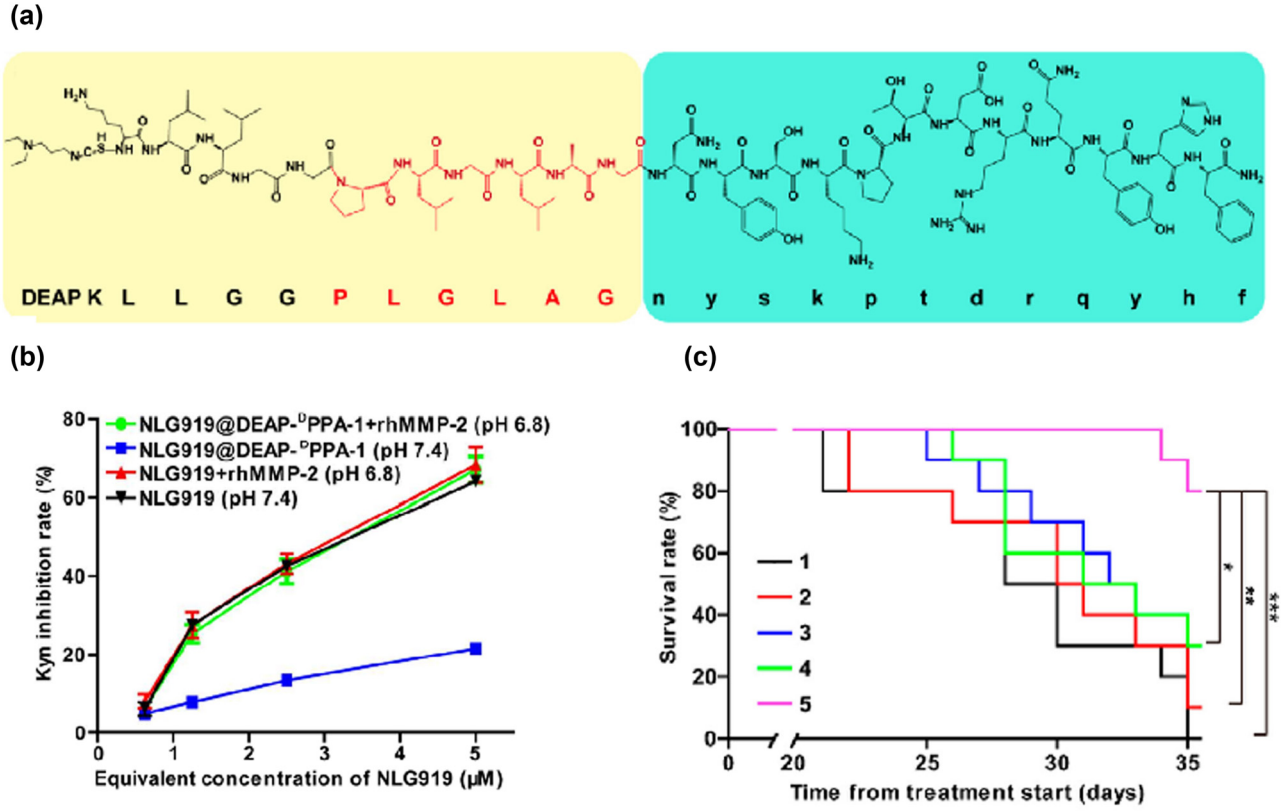

Figure 3: Therapeutic peptide assembling nanoparticle for dual-targeted cancer immunotherapy. (a) Composition of DEAP-DPPA-1. (b) Inhibitory effect of NLG919 and NLG919@DEAP-DPPA-1 nanoparticles on IDO enzyme activity was evaluated by examining the amount of kynurenine (Kyn) in the B16-F10 cell medium. (c) Survival curve of mice treated with various formulations ($n = 10$). Treatment groups: 1, DEAP-^{D}PPA-1-Scr; 2, NLG919; 3, NLG919@DEAP-^{D}PPA-1-Scr; 4, DEAP-^{D}PPA-1; 5, NLG919@DEAP-^{D}PPA-1. Reproduced from Ref. [53]. Copyright 2018, American Chemical Society.

improving survival rate (Figure 3b and c). These studies successfully incorporated nanoparticles into T cell-based immunometabolic therapy and demonstrated the important potential of nanoparticles.

According to the high ROS level in TME, Wan *et al.* designed a ROS-sensitive nanoparticle, which loaded siFGL1 and siPD-L1 [54]. Thioketal (TK), which is ROS-sensitive, and cis-aconitate (CA) form CA-PLL-TK, with the skeleton of the polycationic material ε-poly-L-lysine (PLL). Then siFGL1 and siPD-L1 were loaded through electrostatic adsorption, and were administered with iRGD. After a combination of CA and hydrogen protons, the conformation of the nanoparticle was changed. Then the ROS resulted in the disruption of the nanoparticle structure and the release of siFGL1 and siPD-L1 (Figure 4a–d). The expression of FGL1 and PD-L1 was down-regulated after co-incubation with CPT-NPs/siFGL1/siPD-L1. After the treatment of CPT-NPs/siFGL1/siPD-L1 + iRGD in tumor-bearing C57BL/6 mice, the volume and weight of the tumor decreased, the levels of IL-2, IFN-γ, and TNF-α were elevated, and the number of $CD4^+$ T cell and $CD8^+$ T cell increased. The results suggested that tumor-penetrating peptide iRGD and ROS-responsive nanoparticles can promote the delivery efficiency. To sum up, nanoparticles can load metabolic regulatory drugs and ICIs, and increase clinical efficacy.

2.3 Nanoparticles that combine T-cell metabolism and ACT

ACT has achieved great success in the treatment of malignant tumors, especially hematological malignancies [55,56]. Adoptive T cell from donor would be reinfused back to the patient to attack abnormal cell after experiencing *ex vivo* expansion and engineering [56]. However, ACT still has significant limitations that must be addressed, including

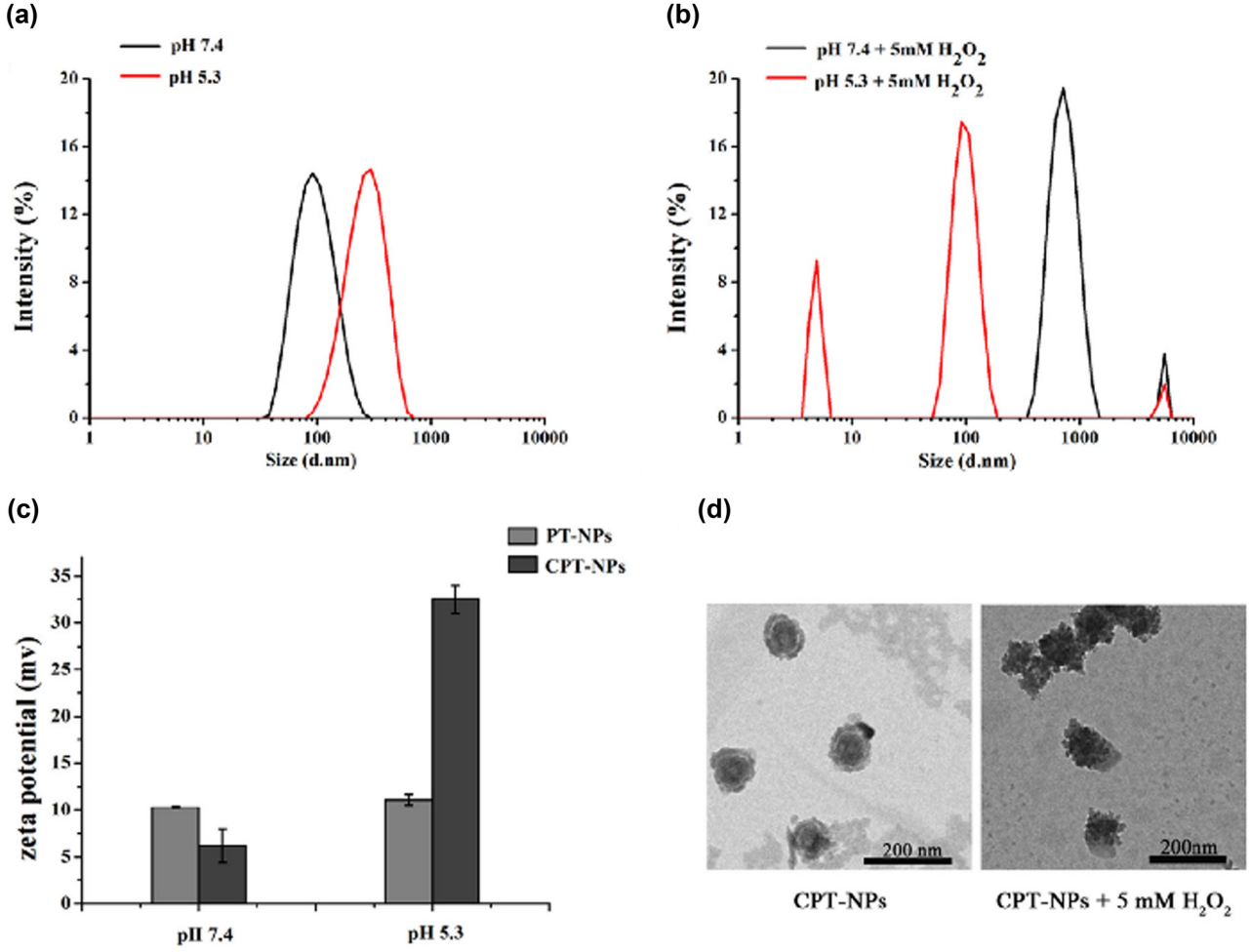

Figure 4: ROS-sensitive nanoparticle loading siFGL1 and siPD-L1. (a) and (b) Size distribution of CPT-NPs in different pH values. (c) Zeta potential changes of CPT-NPs. (d) TEM images of CPT-NPs. Reproduced from Ref. [54]. Copyright 2021, Elsevier.

post-transfer T cell exhaustion and death, limited efficacy in solid tumors, and severe side effects [57,58].

Previous studies have reported that the function of T cell needs the cholesterol on the cell membrane to aggregate the T cell receptor (TCR) and form immune synapses [59–61]. Avasimibe, working as an inhibitor of cholesterol esterase acetyl CoA acetyltransferase 1, can elevate cholesterol concentrations and facilitate TCR clustering, to upregulate the anti-tumor ability of T cell [62]. Hao *et al.* proposed a new strategy to combine the lipid metabolism-modulating drug Avasimibe with adoptive T cell for solid tumor therapy [63]. This novel T cell surface anchoring technology anchored the lipid on the T cell membrane through hydrophobic force, and then coupled the lipid and the drug liposome on the T cell membrane through a click reaction (Figure 5a) [63]. In this process, the researchers constructed bicyclo[6.1.0]nonyne (BCN)-modified Au nanoparticles (BCN-Au), which enabled the drug to be attached on the surface of T cell (Figure 5b). After avasimibe was loaded on the surface of T cell, the physiological function of the T cell was not disturbed. Engineered T cell can increase the cholesterol level of the T cell membrane through the dual effects of "autocrine and paracrine," to promote the rapid aggregation of TCRs and increase the sustained activation of T cell (Figure 5c). Treatment with surface anchor-engineered T cell shows excellent efficacy in *in vivo* experiments, and three of the five

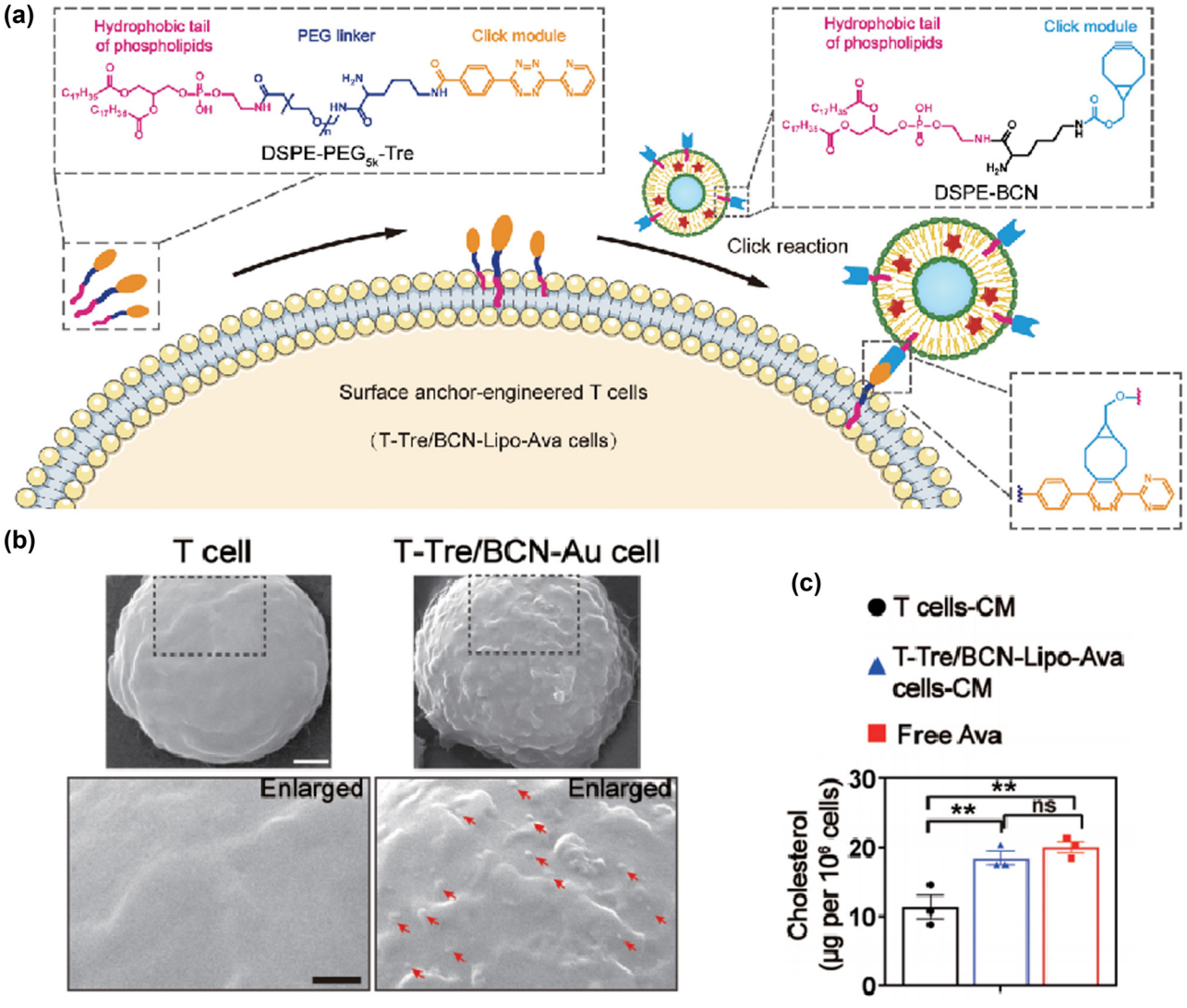

Figure 5: Nanoparticle that combines the lipid metabolism-modulating drug Avasimibe with adoptive T cell. (a) Structures of T-Tre/BCN-Lipo. (b) SEM of a T-Tre/BCN-Au cell and a T cell. Red arrows indicate BCN-Au nanoparticles. White scale bar, 1 μm. Black scale bar, 500 nm. (c) Quantification of plasma membrane cholesterol content in $CD8^+$ T cell. Reproduced from Ref. [63]. Copyright 2020, American Association for the Advancement of Science.

mice completely eradicated glioblastoma [63]. Here, liposomal Avathimide is clicked on the surface of T cell through lipid insertion, without interfering with the physiological function of T cell. This combination strategy results in good curative effects and few toxic side effects.

2.4 Nanoparticles that combine T-cell metabolism and other immune-related therapies

Nanoparticles are also used in combination with T-cell metabolism and other immune-related therapies. Photodynamic therapy (PDT) relies on photosensitizers (PS) to absorb light energy and convert oxygen into cytotoxic ROS to directly kill tumor cell [64,65]. However, the hypoxic state of the TME always affects the efficacy of PDT [66]. Xing *et al.* reported the fluorinated polymeric nanoparticles (PF-PEG NPs) with PS Chlorin e6 (Ce6) and IDO1 inhibitor NLG919 in the hydrophobic core (Figure 6a) [67]. These nanoparticles possess a better oxygen-carrying and longer oxygen retention ability, which can solve the hypoxic state of the TME (Figure 6b and c). Meanwhile, the co-encapsulation of NLG919 and PS can improve T cell infiltration, as well as IFN-γ positive $CD8^+$ T cell, and inhibit tumor growth. In this study, a multi-functional nanoplatform constructed with oxygen-enriched fluorinated polymer nanoparticles with Chlorin e6 and NLG919 was developed to realize the combination of IDO inhibitor and PDT. This work is a successful model of the achievements of nanoparticles in T cell-based immunometabolic therapy and provides clinical benefits in cancer treatment.

3 Clinical application of nanoparticles

With the rapid development, nanoparticles play an increasingly important role in the treatment of malignant tumors [68]. Nanoparticles can change their sizes, shapes, charges, and surface modifications to deliver molecules, thereby improving therapeutic efficacy and reducing side effects, for example, improving vascular dynamics by changing the size and shape of nanoparticles, or avoiding phagocyte absorption using biomimetic membranes [69]. Nanoparticles can also complete the targeted delivery by adding targeted ligands, which is difficult for other traditional delivery systems [70]. The uptake of nanoparticles in tumors is achieved through enhanced permeability and retention effect and the active recognition of targeted ligands by receptors over-expressed at pathological sites [71]. But the clinical transformation of nanoparticles still faces many challenges, including insufficient distribution and accumulation of therapeutic drugs, as well as off-target toxicity in the liver and spleen, which may be caused by non-specific removal by the reticuloendothelial system. The production of nanoparticles usually requires a more complex synthesis process than traditional drugs, which makes it difficult to be produced on a large scale and ensure quality control [71]. Currently, common nanoparticles include polymer nanoparticles, lipidic nanocarriers, protein complexes, metal organic skeleton complexes, and inorganic nanoparticles.

Poly lactic-co-glycolic acid (PLGA) is an FDA approved biodegradable polymer nanoparticle [72]. PLGA molecule contains lactic acid (LA) and glycolic acid (GA), and the LA/GA ratio can affect the stability and degradation time of

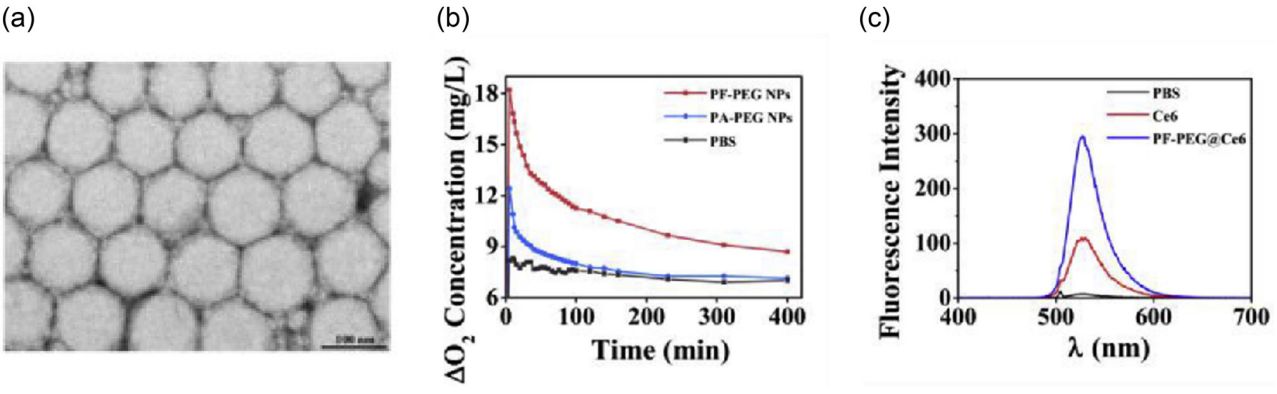

Figure 6: Nanoparticle loading Ce6 and NLG919. (a) TEM image of PF-PEG@Ce6@NLG919 NPs. (b) Dissolved oxygen release curves of PF-PEG NPs, PA-PEG NPs, and PBS. (c) Oxygen dissolution of PBS, Free Ce6, and PF-PEG@Ce6 NPs showed a 3-fold enhancement of PF-PEG@Ce6 compared with Ce6. Reproduced from Ref. [67]. Copyright 2019, Elsevier.

PLGA [73]. PLGA has good biocompatibility and biodegradability, controllable degradation rate, but its loading capacity is low, especially for hydrophilic and/or amphiphilic small molecules [74].

Liposomes are spherical lipidic nanocarriers composed of a lipid bilayer with phospholipids and cholesterol, forming an amphipathic nano/micro-particle [75], which have been used as an important nano-delivery system [76]. Abumanhal-Masarweh *et al.* constructed liposomes loaded with sodium bicarbonate, and combined them with doxorubicin to treat TNBC (Figure 7a and b) [77]. The combination therapy can modulate the tumor pH (Figure 7c), promote the infiltration of immune cell, T cell, B cell and macrophage in TME, and inhibit tumor progression [77]. Liposomes are one of the most successful nanodelivery systems, and a variety of liposomes have been approved by FDA [75,76]. Therefore, liposomes have a great application prospect in T cell-based immunometabolic therapy.

Inorganic nanoparticles can obtain appropriate dispersion through surface modification, and additional functions can be performed [78]. For example, capsule containing gold nanoshells can respond to near-infrared light to facilitate on-demand drug release [79]. Typical inorganic nanoparticles include gold, iron oxide, silver, or silica. The main reasons for the limited clinical application of inorganic nanoparticles are low solubility and toxicity [78].

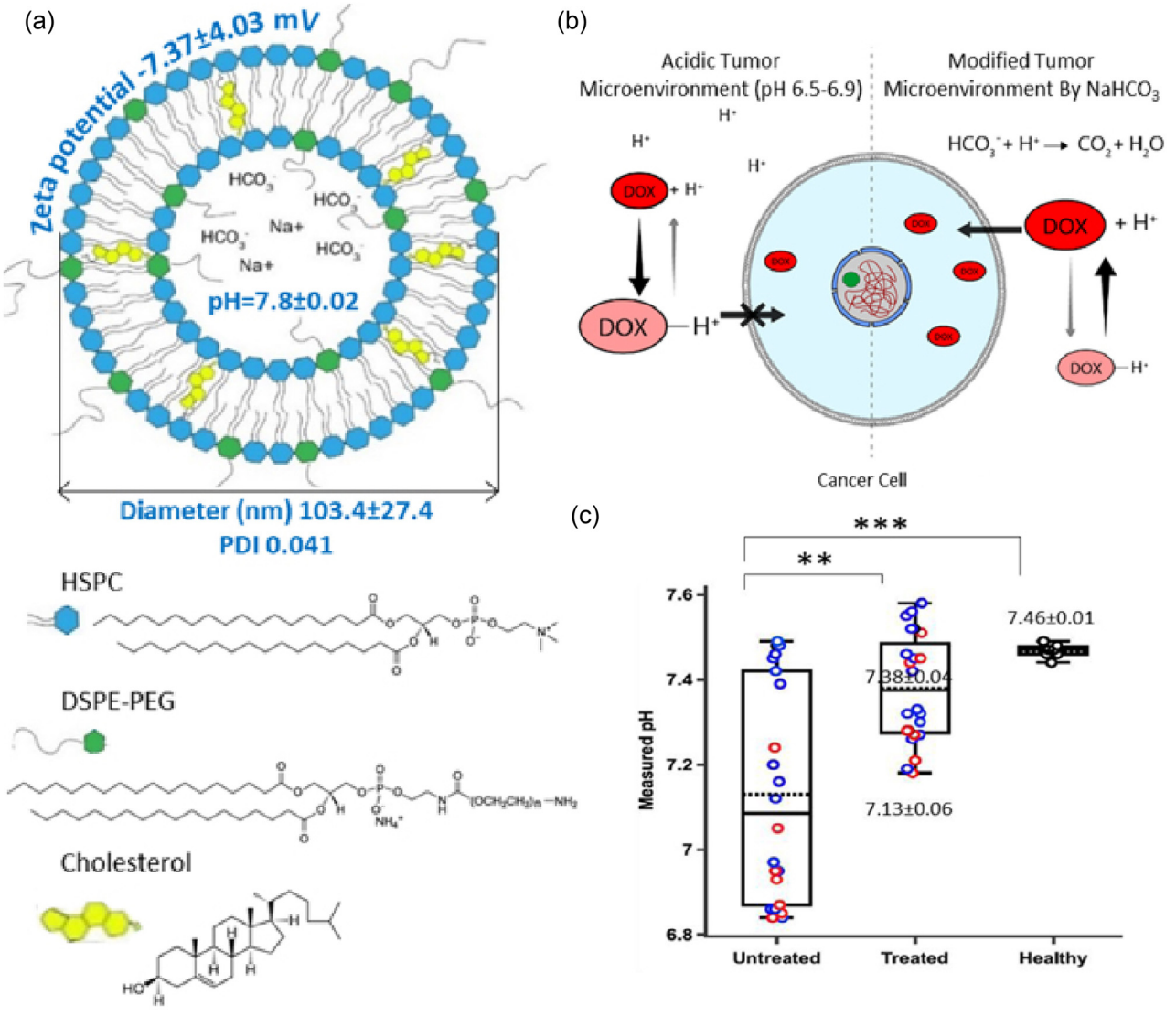

Figure 7: Liposomes loaded with sodium bicarbonate and doxorubicin. (a) Liposomes encapsulating sodium bicarbonate were constructed of hydrogenated soybean phosphatidylcholine, cholesterol, and PEG-distearoyl-phosphoethanolamine. (b) Schematic diagram of the effect of pH on the efficacy of doxorubicin. (c) The pH value was 7.38 ± 0.04 in the liposomal bicarbonate-treated group, 7.13 ± 0.06 in the untreated tumor, and 7.46 ± 0.01 in healthy mammary fat pad. Reproduced from Ref. [77]. Copyright 2019, Elsevier.

Due to the unique properties, the application of nanoparticles has been gradually explored in T cell-based immunometabolic therapy. Table 1 shows various representative nanoparticles that combined T cell metabolism and T cell-based immunotherapy. Despite the enormous potential of nanoparticles in cancer therapy, they are in the relatively early stages of clinical applications.

4 Future perspectives

Immunotherapy aims to activate immune cells to kill and eliminate tumor cells, and metabolic reprogramming in TME can induce immune cell dysfunction and decrease the response to immunotherapy. In the last few years, tremendous advances have been made in T cell-based immunometabolic therapy, but the complexity of the TME increases the difficulty of drug delivery. To implement T cell-based immunometabolic therapy, nanoparticles can be used as a scientific and practical drug delivery system. In this review, the recent process of using nanoparticles in the T cell-based immunometabolic therapy is analyzed and prospected.

Nanoparticles possess excellent performance in targeted drug delivery, stimulated reactive drug release, and delivery of combination drugs. With the assistance of nanoparticles, researchers developed new therapies to regulate metabolism in combination with immunotherapy. We discussed several representative nanoparticles in the T cell-based immunometabolic therapy, and found that they all demonstrated excellent efficacy. Meanwhile, we are aware that some issues remain to be addressed to achieve clinical translation: (1) research on metabolic reprogramming provides theoretical basis, (2) nanoparticles need to be carefully designed for safety requirements, and (3) targeted delivery is helpful to improve effectiveness (Figure 8).

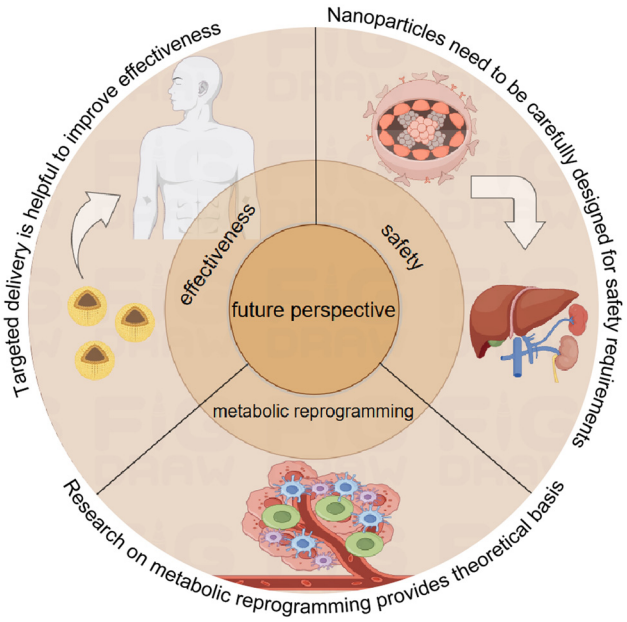

Figure 8: Future perspective of nanoparticles in the T cell-based immunometabolic therapy. The figure is drawn by Figdraw.

First, the influence of metabolic reprogramming on immunotherapy and the relative mechanism are complex and require further exploration. The metabolism of immune cells and cancer cells in TME is interdependent. Cancer cells consume nutrients and produce immunosuppressive metabolites, thus promoting malignant progression. We reported that in cervical cancer, 7-dehydrocholesterol reductase (DHCR7), an enzyme that catalyzes the last step of cholesterol synthesis, was upregulated and closely related to the prognosis [80]. DHCR7 can promote lymph node metastasis in cervical cancer through cholesterol reprogramming in TME [80]. However, many other effects and mechanisms of metabolic reprogramming remain unclear. In-depth study can provide more theoretical basis for using nanoparticles in the T cell-based immunometabolic therapy.

Table 1: Representative nanoparticles in the T cell-based immunometabolic therapy

Delivery system	Combined therapy	Drug	Metabolite	Tumor type	Ref.
aCD3/F/AN	Activation of T cells	Fenofibrate	Lipid	Melanoma	[49]
NLG919@DEAP-DPPA-1-Scr	ICI	Amphiphilic peptide, NLG919	Tryptophan	Melanoma	[53]
CPT-NPs/siFGL1/siPD-L1 + iRGD	ICI	siFGL1, siPD-L1	ROS	Lung cancer	[54]
T-Tre/BCN-Lipo	ACT	Avasimibe	Cholesterol	Glioblastoma	[63]
PF-PEG@Ce6@NLG919	Other therapy	NLG919, photosensitizers	Tryptophan	Breast cancer and cervical cancer	[67]
Liposomal doxorubicin plus liposomal bicarbonate	Other therapy	Sodium bicarbonate	PH	Breast cancer	[77]

Second, the safety concern of nanoparticles is one of the core issues in the application of nanoparticles in the T cell-based immunometabolic therapy. The trials of nanoparticles in immunotherapy have been carried out in large numbers over recent years. In sharp contrast, very few nanoparticles have been used clinically so far. Nanoparticles are accumulated in the lungs, spleen, kidney, liver and heart, and are difficult to remove, which raises concerns about the safety of nanoparticles. The chemical composition, size, shape, specific surface area, and surface charge of nanoparticles need to be carefully designed for safety requirements, and directly affect the scale and difficulty of nanoparticle production.

Third, the distribution of nanoparticles can directly affect their effectiveness in T cell-based immunometabolic therapy. Metabolic competition in the TME can also affect the delivery of nanoparticles. Therefore, how to achieve targeted delivery and controlled release performance is one of the current research difficulties. In order to solve these difficulties, we can design the nanoparticles based on the metabolic characteristics of TME, such as hypoxia, acidity, and high ROS. The targeted modification of nanoparticles can also be achieved using ligands or antibodies with specific recognition capabilities to improve the distribution and enrichment of nanoparticles *in vivo*. Imaging technology can track the dynamic distribution and enrichment of nanoparticles in the T cell-based immunometabolic therapy.

As this review indicates, T cell-based immunometabolic therapy holds great promise, and nanodelivery system can solve the problems of pharmacokinetic inconsistencies and bioutilization difficulties. There are still many difficulties that need to be overcome in the clinical translation of nanoparticles in T cell-based immunometabolic therapy.

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