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Advances in nanomaterial-based targeted drug delivery systems

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Nanomaterial-based drug delivery systems (NBDDS) are widely used to improve the safety and therapeutic efficacy of encapsulated drugs due to their unique physicochemical and biological properties. By combining therapeutic drugs with nanoparticles using rational targeting pathways, nano-targeted delivery systems were created to overcome the main drawbacks of conventional drug treatment, including insufficient stability and solubility, lack of transmembrane transport, short circulation time, and undesirable toxic effects. Herein, we reviewed the recent developments in different targeting design strategies and therapeutic approaches employing various nanomaterial-based systems. We also discussed the challenges and perspectives of smart systems in precisely targeting different intravascular and extravascular diseases.

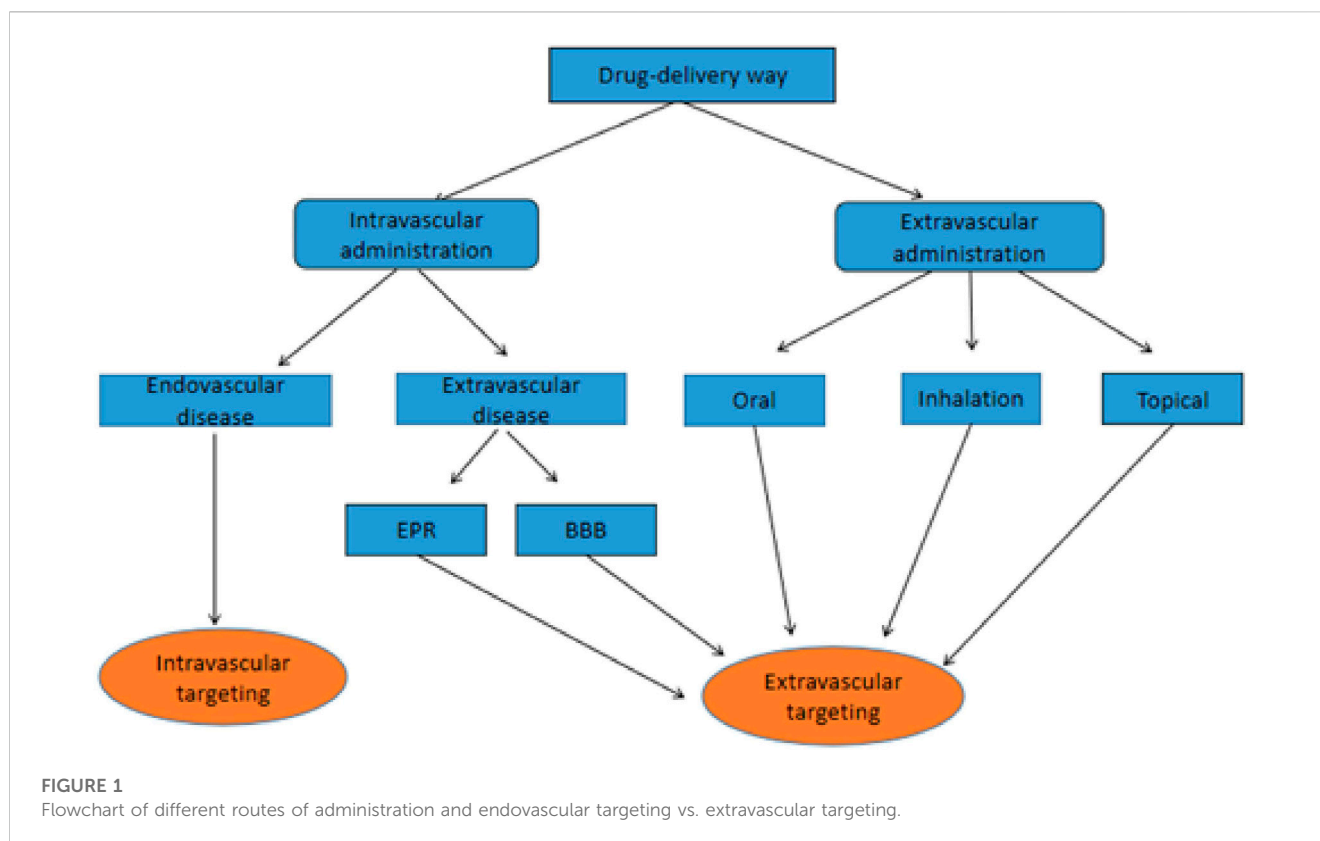
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1 Introduction

In the past few years, the successful development of nanotechnology, especially the emergence of new nanomaterials, has provided new ideas and potential methods for diagnosing and treating many major diseases (Kinnear et al., 2017; Miguel et al., 2022). Because of their unique physicochemical and biological properties, nanomaterials are widely used in drug delivery systems (DDS). Compared to conventional DDS, nano-DDS can effectively enhance the therapeutic efficacy by improving the pharmacokinetic and pharmacodynamic properties of encapsulated drugs, including drug stability, and achieving targeted drug delivery and controlled drug release due to their special characteristics of size, shape, and material (Yetisgin et al., 2020).

Targeted drug delivery refers to successfully targeting therapeutic agents and their primary accumulation at the desired site. Combining therapeutic drugs with nanoparticles and designing suitable targeting pathways is a promising targeted drug delivery method that can deliver many molecules to specific locations in the body (Jahan et al., 2017). To achieve high targeting efficacy, the DDS must be retained in the physiological system for an appropriate time to target specific cells and tissues to release the delivery drug, avoiding its destruction by the immune system (Davis et al., 2008). Nanoparticles can improve the stability and solubility of encapsulated cargo, facilitate transmembrane transport, and prolong cycle times, thereby improving safety and effectiveness (Kou et al., 2018). Nanoparticles can enter the bloodstream through blood vessels and then act at specific sites within the blood vessels to treat intravascular diseases, which is called intravascular drug delivery. Nanoparticles can also cross the endothelium of blood vessels or reach target tissues through local administration such as oral, inhalation, subcutaneous administration, etc., which is called extravascular drug delivery (Figure 1). However, the precise delivery of therapeutic drugs to the target area remains an important issue that needs further



investigation to enhance the treatment efficiency of various diseases. In this review, we discuss the design features and therapeutic approaches of different nanomaterials according to the targets of nanomedicines: intravascular and extravascular diseases (Table 1). We also explore some of their limitations and provide an outlook on future directions for targeted drug delivery.

2 Intravascular targeting nanoparticles

Within the past 10 years, the DDS targeted to intravascular diseases has been widely used as a prospective treatment method, including cancers and cardiovascular diseases. Adult blood vessels cover a surface area of 43,000 to 75,000 square feet. However, only a small part of this surface area is affected by vascular disease, showing local inflammation (Davies et al., 2013; Zhou et al., 2014; Gimbrone and García-Cardeña, 2016). Reduction of vascular inflammation by systemic drug therapy usually increases pathogen infection and delays tissue repair (Ridker et al., 2017). Therefore, nanomaterials can be used as vascular-targeted carriers for intravascular drug delivery, reducing the side effects caused by systemic drugs through local targeting. The altered local environment caused by intravascular inflammation can provide ideas for the design of nanoparticles. Increased inflammatory factors, immune cells, and receptors on immune cell membranes all become targets for nanoparticles. Nanoparticles are often modified for intravascular targeting, such as binding peptides, antibodies, and other ligands, coating the surface with cell membranes, and binding the nanoparticles to external physical stimuli. These modification

techniques are also commonly combined to enhance the vascular targeting of nanoparticles.

2.1 Surface modification and active targeting

The surface of nanocarriers is specifically modified to enter the vascular system and bind to markers on the vascular wall to release the loaded drug for local therapeutic effects (Kelley et al., 2016). This disease-site-specific release increases the drug efficacy and reduces side effects due to systemic administration. It has been reported that the ability to target ligands to nanomaterials enables cell specificity of therapeutic genes/drugs (Arias et al., 2018; Yang et al., 2018; Aizik et al., 2020; Lockhart et al., 2021). Additionally, the vascular endothelium is an effective target for vascular-targeted therapy. The vascular endothelium comprises endothelial cells and vascular lumen and significantly participates in tissue fluid balance and vascular homeostasis (Aird, 2008; Rafi et al., 2016).

Endothelial dysfunction is the root cause of many diseases such as atherosclerosis, major cardiovascular diseases (peripheral artery disease, coronary artery disease, stroke, and myocardial infarction) (Libby et al., 2002; Hansson, 2005), sepsis, acute respiratory distress syndrome (Lee and Slutsky, 2010; Matthay et al., 2012) and COVID-19 respiratory distress (Matthay et al., 2012). Locally disrupted blood flow can significantly enhance the expression of vascular cell adhesion molecule 1 (VCAM-1). Evident high and low VCAM-1 levels are also observed in inflamed and healthy endothelium, respectively (Davies et al., 1993; Nakashima et al., 1998). Zhou et al. designed a VCAM1-targeting polyelectrolyte complex micelles

TABLE 1 The design of nano-DDS in endovascular and extravascular targeting.

Targeting type	Nanosystem	Drugs	Targeting moieties	External stimuli	Key design features	Clinical translation	References
Intravascular targeting	VCAM-1-targeting polyelectrolyte micelle	miR-92a inhibitor	Inflamed ECs		Nucleotide-based therapies; polyelectrolyte complex micelles protect the nucleic acids from enzymatic degradation	None	Zhou Z. et al. (2021)
	VHPK-conjugated-pBAE NPs	Anti-miR-712	Inflamed ECs		Overexpression of miR-712 leads to endothelial dysfunction and AS	None	Dosta et al. (2021)
	PEG-b-PLGA copolymer-based NP	CRISPR-Cas9 plasmid DNA	Vascular ECs		NP delivery CRISPR plasmid DNA under the control of the Cdh5 promoter; genome editing in the ECs	None	Zhang X. et al. (2022)
	fAuNPs	DMXAA	Tumor vessels	PTT	DMXAA enhance the local trapping of gold NPs; increased effectiveness of photothermal	None	Hong et al. (2020)
	RGD@HCuS(VA)	VA	ECs	NIR laser	N ₂ bubbles released by NIR radiation to induce tumor cell necrosis	None	Gao W. et al. (2017)
	Th-Dox-NPs	Thrombin and Dox	Tumor-vessel walls and tumor stroma		Active tumor tissue-targeting ability; cutting of the blood supply by thrombus and inhibiting tumor cell proliferation; synergistic treatment of embolization therapy and chemotherapy	None	Li S. et al. (2020)
	Leukosomes		Inflammatory vascular		Reduced RES uptake; adhesion to inflamed endothelium	None	Martinez et al. (2018)
	Leukosomes	Rapamycin	Atherosclerotic plaques		High histocompatibility; stable drug release efficiency	None	Boada et al. (2020)
	RBC-membrane-camouflaged polymeric NP		Vascular		Long blood retention time	None	Hu et al. (2011)
	PNP	Rapamycin	Atherosclerotic plaques		Reduce the phagocytosis of NPs by macrophages	None	Song et al. (2019)
	Neutrophil cell-membrane-formed nanovesicles		Vascular inflammation		Nanovesicles can improve the specificity and affinity to the target; reduce the lung inflammation and edema	None	Gao et al. (2016)
	H ₂ O ₂ /PFP phase-change NPs		Thrombolysis	US	Oxygen release under ultrasound application	None	Jiang et al. (2020)
	PHPMR NPs	MnFe ₂ O ₄ , HMME, PFP	ECs	US, SDT	High ROS production efficacy under US and SDT	None	Yao et al. (2021)
SWNTs		Immune cells	PAI	Utilized PAI-active nanomaterial agents assess immune cells migration into tumors	None	Gifani et al. (2021)	
Extravascular targeting	Dox/F127&P123-Tf	Dox	Tumor cells		DOX/F127&P123-Tf can inhibit cell migration and change the cell cycle	None	Soe et al. (2019)
	FDMCA	MIP-3β plasmid	Immune cells in tumor		Targeted gene delivery system to polarize macrophages toward M1, inhibiting tumor growth	None	He et al. (2020)
	⁶⁴ Cu-GE11 PMNPs		HCT116 colon cancer cells		⁶⁴ Cu-GE11 PMNPs have a desirable prolonged residence time in the blood pool and a	None	Paiva et al. (2020)

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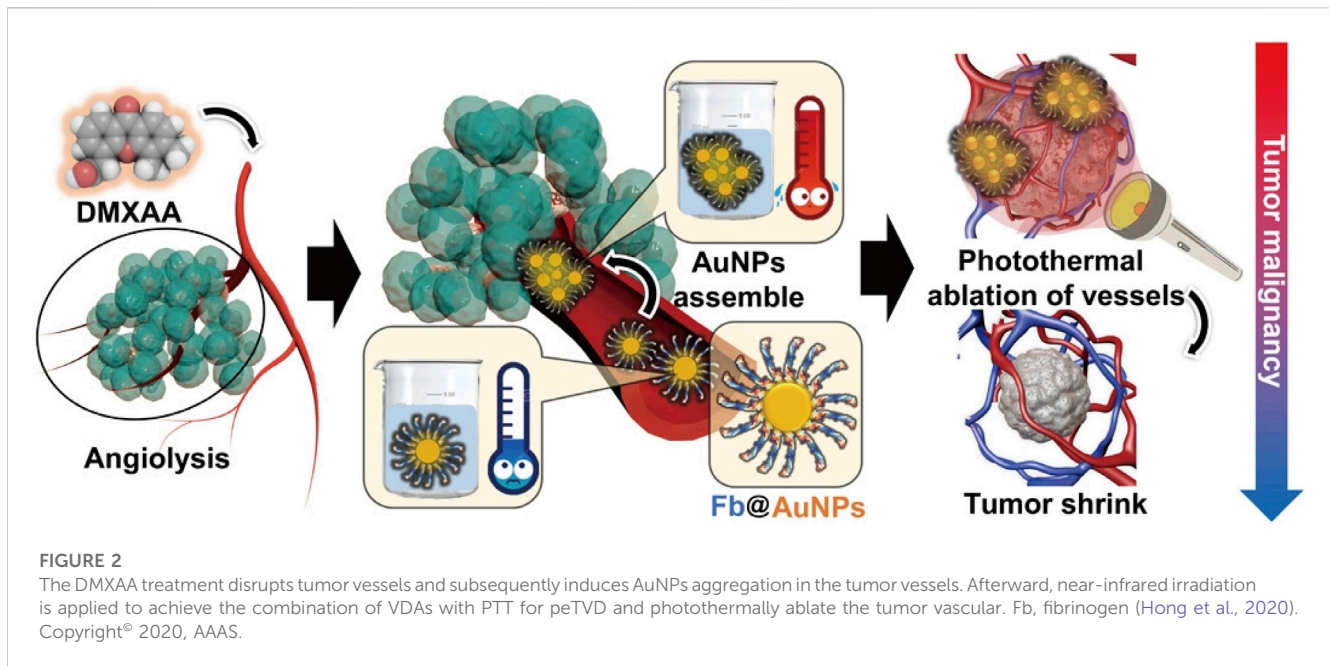
TABLE 1 (Continued) The design of nano-DDS in endovascular and extravascular targeting.

Targeting type	Nanosystem	Drugs	Targeting moieties	External stimuli	Key design features	Clinical translation	References
					significant uptake in EGFR-expressing tumor tissue		
	TLS11a-LB@TATp-MSN/DOX	DOX	Nuclei of H22 cells		NPs contained liver cancer-specific aptamer TLS11a and nuclear localization peptide TATp to locate the nucleus	None	Ding et al. (2020)
	PM@CDDP/SNP	Cisplatin and sodium nitroprusside	Tumor		PMCS selectively induced ONOO ⁻ generation after a cascade responding high levels of NOXs and GSH in tumors	None	Chen Y. et al. (2021)
	Col-TNPs		ECM		Col-TNPs deliver collagenase to degrade collagen in tumors, enhancing the intracellular transcytosis of TNPs	None	Wang et al. (2022)
	siFAK + CRISPR-PD-L1-LNPs	FAK siRNA, Cas9 mRNA and sgRNA	TME		Enhanced gene editing efficiency by altering the mechanical properties of the tumor microenvironment	None	Zhang et al. (2022a)
	PLP-D-R	DOX and antiplatelet antibody R300	Tumor vessels		MMP2 can promote the release of R300 in NPs, which can consume platelets and improve tumor vascular permeability	None	Li S. et al. (2017)
	GE11-PDA-Pt@USPIOs	Cisplatin, poly dopamine	EGFR-positive tumor cells	MRI/PAI	The thick PAA coating allows highly efficient cisplatin; the thin PDA coating endows the particles with photo-thermal properties	None	Yang et al. (2019)
	PEG-TK-DOX	DOX, PhA	The tumor	PDT	The production of exogenous ROS during PDT, leading to a further ROS cascade that accelerates the release of DOX and PhA in NPs	None	Kim et al. (2020)
	IT-TQF NPs	IT-TQF	The tumor	PTT	First phototheranostic agent; outstanding optical and photothermal properties	None	Lou et al. (2022)
	MMP sensitive liposomes coated with PEG		ECM of the tumor	US	The combined use of US and microbubbles can increase the penetration depth of liposomes into the extracellular matrix	None	Olsman et al. (2020)
	FCNPs		Vessels	pHIFU	pHIFU can reduce irreversible thermal effects by reducing the average intensity of US	None	You et al. (2017)
	⁸⁹ Zr-NRep	DOX	Tumor vessels	EP	⁸⁹ Zr-NRep can be used to monitor the effects of electroporation and predict RE-mediated uptake of nanoparticle therapeutics <i>in vivo</i>	None	Srimathveeravalli et al. (2018)
	pHA-αPDL1	α-PDL1	Brain and the glioma		pHA-αPD-L1 can activate T cell immune response and relieve immunosuppressive TME	None	Guo et al. (2020)
	TfR-targeting liposomes	Cisplatin	ECs	FUS	The use of FUS in combination with	None	Olsman et al. (2021)

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TABLE 1 (Continued) The design of nano-DDS in endovascular and extravascular targeting.

Targeting type	Nanosystem	Drugs	Targeting moieties	External stimuli	Key design features	Clinical translation	References
					intravascular MBs can increase in BBB permeability		
	PLGA-PEG NPs		Intestinal epithelium		Albumin engineered enhanced receptor binding and transcellular transport of NPs	None	Azevedo et al. (2020)
	MOF-Gel NPs	Exendin-4	Intestinal epithelium		Neutral PH encouraged sodium bicarbonate and citric acid to dissolve and reacted with CO ₂ , thus facilitating the release of NPs from the capsules	None	Zhou Y. et al. (2021)
	Polypeptide/siRNA polyplexes	siRNAs	Mucus layer and cell membrane		Fluorination of the cationic polypeptides potentiated the mucus-penetration capability; first example of transmucus gene delivery by using the fluorination approach	None	Ge et al. (2020)
	Tf-AMQ NPs	AQ	NSCLC cell		Cytotoxicity studies shown reduction in IC ₅₀ values with Tf-AMQ NPs; AQ's autophagy inhibition ability increased in Tf-AMQ NPs	None	Parvathaneni et al. (2021)
	AG@MSNs-PAA	AG	OA		PAA degraded in an acidic environment, releasing AG to restore IL-1 β -induced chondrocyte apoptosis	None	He et al. (2021)
	BNPs	EB	Peritoneal carcinomatosis		The BNPs with abdominal tissue extended the retention after i.p. injection; EB can against multiple PTX-sensitive <i>in vitro</i>	None	Deng et al. (2016)
		EB	Glioblastoma		NPs with 'stealth' properties can avoid internalization by all cell types	None	Song et al. (2017)
		CPT	SCC tumor cell and matrix proteins		The encapsulation of CPT within BNPs enhanced the delivery of CPT, ; chemotherapy may be beneficial in immune suppression	None	Hu et al. (2021)
		EVG	Vaginal lumen		BNPs can penetrate mucus and once in contact with epithelial cells or leukocytes, they become immobilized and are retained for long periods	None	Mohideen et al. (2017)
	DES-MSNs		Skin penetration		DES-MSNs could drive the MSNs to penetrate across the entire skin via a "Drag" effect; transdermal delivery of the MSNs into blood circulation	None	Zhao et al. (2022)
	CAT-TCPP/FCS NPs	CAT-TCPP	Intratumoral	SDT	Non-invasive excitation of PS in orthotopic bladder; tumor hypoxia amelioration triggered by the O ₂ production of tumoral endogenous H ₂ O ₂ catalase	None	Li G. et al. (2020)
	P/B-COS NPs	BUD	Myocardium	RF	Local high temperature in RF promoted local rupture of NPs, releasing BUD	None	Liu et al. (2022)



targeting inflammatory vascular endothelium, which could efficiently deliver therapeutic nucleotides to inflammatory endothelial cells (Zhou Z. et al., 2021), similar to (Dosta et al., 2021).

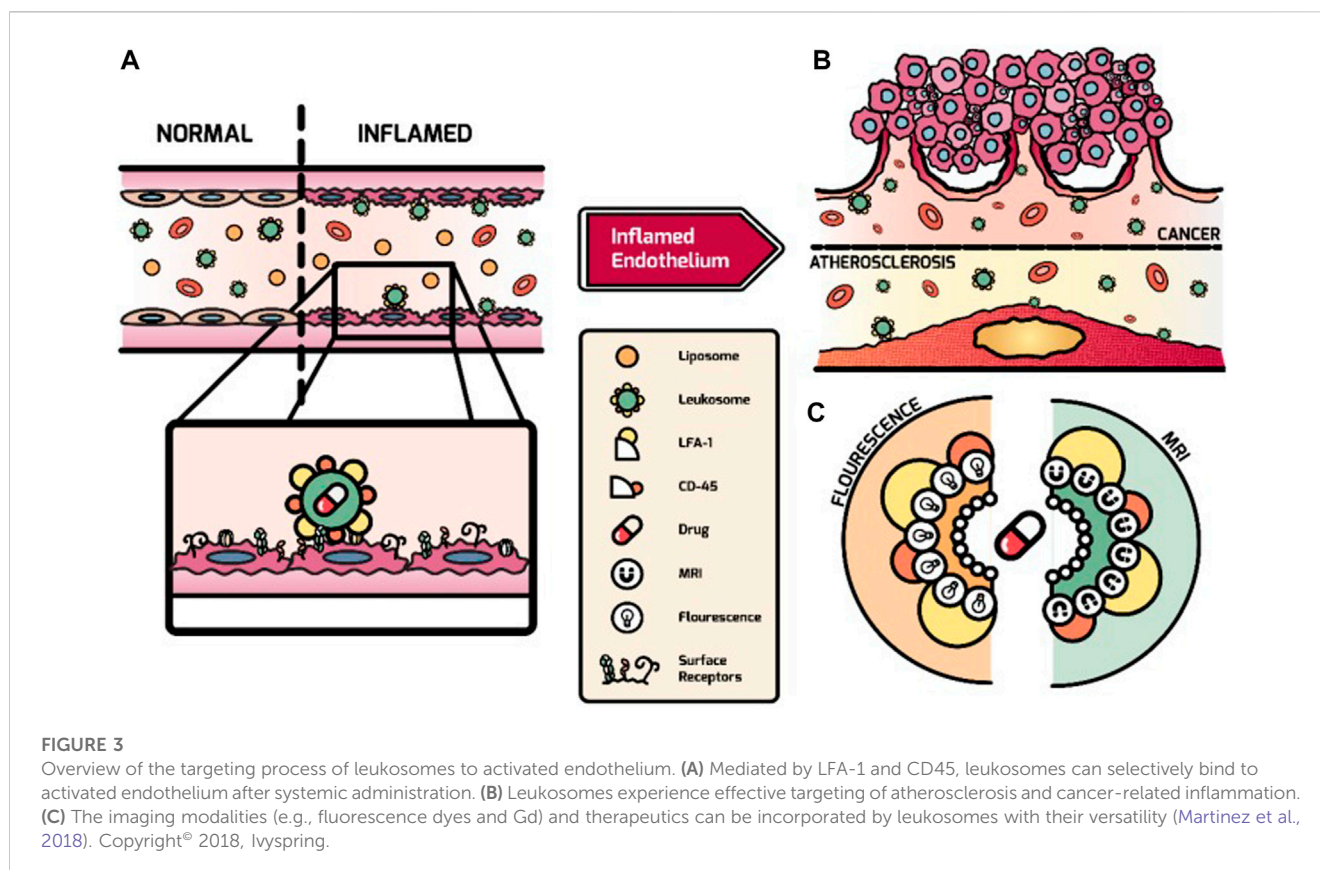
Gene editing of endothelial cells (ECs) is also a promising therapeutic approach. Recently, a novel delivery system using genome editing was developed by Zhang X. et al. (2022) for vascular Ecs. Exogenous genes can be introduced to inhibit vascular injury and/or promote vascular repair, and gene editing systems can be delivered to correct gene mutations and turn specific genes on or off. The nanoparticles carrying CRISPR-Cas9 gene editing plasmids induced efficient gene editing in Ecs of mouse vasculatures, as well as peripheral blood vessels, aorta, heart, and lung. Consistent with the phenotype of genetic knockout mice, significantly decreased levels (80%) of the protein encoded by PI3KCG in EC as selectively observed using immunofluorescent staining and Western blotting. This delivery system represents an important breakthrough in the treatment of diseases caused by endothelial dysfunction, as well as cardiovascular research. Local inflammation usually occurs in intravascular diseases such as atherosclerosis. Inflammation is a body's natural and necessary response to tissue damage. The enhanced EPR effect occurs at inflamed vessels (Tu et al., 2022), perhaps this is one of the reasons for facilitating the passage of nanoparticles through the vascular endothelium to reach the subendothelial lesions. The High levels of reactive oxygen species (ROS) and low pH in the inflammatory environment can also serve as conditions to trigger the response of nanomaterials (Tu et al., 2022).

However, in the cardiovascular system, the transport of drug-loaded nanocarriers to the target site occurs under dynamic conditions, such as blood flow and its related hemodynamics (Fromen et al., 2016; Ta et al., 2018). Shear stress is also associated with blood flow and plays an important role in the cardiovascular system. Changes in the shear pattern and magnitude are commonly found in cardiovascular and bleeding diseases (Wang Y. et al., 2021). This physiological resistance should

be considered for active modification of vascular-targeted carriers. Several studies have recently investigated targeted functionalized nanoparticles under shear stress conditions *in vitro* to address this challenge (Martínez-Jothar et al., 2020; Zukerman et al., 2020). Zukerman et al. used *in vitro* microfluidic perfusion models to investigate the adhesion of nanoparticles to the endothelium of inflammatory blood vessels under pathological high shear conditions (>70 dyne/cm²). Their results suggested that, under high shear stress conditions, nanoparticles can act as activated endothelial ligands, such as anti-ICAM-1 antibody, E-selectin-binding peptide (Esbp), or their combination and selectively target activated endothelial cells (Zukerman et al., 2020).

The shear stress of blood flow can act as resistance and a driving force for drug release from nanomaterials. Shear-sensitive nanomaterial drug delivery systems have been increasingly investigated, as well as their therapeutic potential to treat hemorrhages and cardiovascular diseases. As major drug carriers triggered by shear stress, shear-deformable nanoparticles can release the drug according to their physical deformation. Recently, using spherical liposomes, Molloy et al. tested the drug release induced by shear. They achieved site-directed delivery of the antiplatelet drug eptifibatide using shear-sensitive phosphatidylcholine (PC)-based nanocapsules to inhibit platelet aggregation at stenotic sites. Moreover, *in vitro* experiments have shown that, under shearing activation, anti-thrombotic drugs can be delivered by these nanoparticles along with the flowing of liposomes-contained whole blood over collagen matrix at different shear rates. Additionally, *in vivo* studies with mice have found that the drug carrier can target high-shear areas. Decreased thrombus formation without prolonging systemic bleeding was also observed (Molloy et al., 2017).

Targeting tumor vasculature can also be a potentially effective therapeutic strategy to inhibit primary tumors and metastasis. Angiogenesis is critical for tumor cell proliferation, invasion, and metastatic spread during solid tumor development. Angiogenesis



involves forming and remodeling new blood vessels that supply tumors with oxygen, nutrients, and growth factors (Wagner et al., 2015). It is also closely related to tumor development and distant metastasis. Therefore, inhibiting tumor angiogenesis has become a new strategy for tumor treatment. Binding targeted ligands (e.g., antibodies or peptides) on the surface of nanomaterials allows them to bind to receptors specifically expressed in tumor vessels but not in healthy tissue. Active targeting results in higher local intravascular concentrations of nanoparticles and increased retention time in leak-free tumor tissues compared to non-targeted forms (Golombek et al., 2018). DMXAA (5,6-dimethylxanthenone-4-acetic acid ASA404) is a typical small-molecule tumor vascular disrupting agent (VDA) in current clinical trials. It can selectively disrupt tumor blood supply, destroy the tumor vasculature, and target the tumor vascular endothelium, resulting in tumor cell ischemic necrosis. DMXAA can also induce the activation of coagulation cascade reaction and rupture of tumor vessels, enhancing the assembly of soluble fibrinogen into insoluble gel-like fibrin in the tumor vessels. Additionally, Hong et al. (2020) prepared fibronectin-conjugated AuNPs (fAuNPs), which were used with DMXAA for tumor vascular disruption therapy (Figure 2). Guided by DMXAA, fAuNPs aggregated at tumor vessels, and further photothermal treatment was performed to enhance the destruction of tumor vessels. Meanwhile, Gao et al. designed a “nanobomb” RGD@HCuS (VA) targeting tumor vascular endothelium. With the *in vitro* irradiation of the NIR laser, the elevated local temperature triggered the rapid release of N₂ bubbles from nanoparticles. These N₂ bubbles exploded instantaneously, destroying the neovascularization

and inducing necrosis of surrounding tumor cells. Due to the modification of RGD peptide on the surface of nanoparticles, it binds to $\alpha\beta_3$ receptors on the vascular endothelium to achieve precise destruction of tumor neovascularization without damaging normal tissues (Gao W. et al., 2017). Tumor vascular infarction can also inhibit tumor angiogenesis. Researchers have conducted numerous studies on tumor vascular infarction, which have yielded excellent tumor treatment effects in animal experiments (Shi et al., 2018; Li S. et al., 2020). A recent study reported combining tumor embolization therapy and chemotherapy with chitosan-based polymeric nanoparticles (Th-Dox-NPs). The nanoparticles were modified with CREKA peptides targeting fibrin–fibronectin complexes overexpressed in tumor vessel walls and stroma. The chemotherapeutic agent doxorubicin (Dox) and the coagulation-inducing protease thrombin were also encapsulated. The authors confirmed the ability of Th-Dox-NPs to induce tumor vascular thrombosis due to the action of thrombin using animal experiments and histological analysis. Compared to nanoparticles delivering only thrombin or Dox, Th-Dox-NPs significantly inhibited tumor growth and recurrence after injection and did not cause somatic toxicity (Li S. et al., 2020). This study provided a paradigm for vascular embolization-based tumor therapy by enabling payload and protease co-delivery through biodegradable tumor-targeting nanoparticles that cause embolization of tumor blood vessels to achieve effective tumor inhibition. Usually, tumor infarction can be acutely induced, and its effects can occur within a few hours (Jahanban-Esfahlan et al., 2017).

2.2 Biomimetic modification and homologous targeting

Once nanomaterials enter the human body, they encounter a complex physiological environment and immune defense system that actively identifies and removes substances unfamiliar to the human body (Moyano et al., 2016; Bourquin et al., 2018). One of the major obstacles is that nanoparticles are absorbed and cleared by the reticuloendothelial system before reaching their targets, to the extent that few nanoparticles loaded with targeting ligands make it through Phase III clinical trials (Hu et al., 2017; Mo et al., 2018; Gao et al., 2020). Therefore, developing biomimetic nano-delivery systems that effectively evade clearance by immune capture and have better targeting capabilities for long-term blood circulation is crucial (Chen et al., 2019). In particular, the use of cell membrane-modified nanoparticles of inflammatory cells is not only effective in avoiding immune capture, but also in achieving better aggregation of inflammatory regions. Such cell-derived nanoparticles can transfer phospholipid bilayers and membrane proteins from cell membranes to nanocarriers, which enables better biocompatibility and targeting of nanoparticles under natural cell membrane camouflage (Fang et al., 2014; Narain et al., 2017).

Biomimetic nanoparticles covering immune cell membranes, such as leukocytes and macrophages, are widely used to treat vascular injury, inflammation, and cancer (Wang et al., 2015; Martinez et al., 2018; Boada et al., 2020; Gao et al., 2020; Wu et al., 2020; Liu et al., 2021). Leukocyte and macrophage membranes are the most attractive materials for biomimetic DDS. As the main cellular components of innate immunity, leukocytes and macrophages can be better recruited and accumulated into vascular inflammatory cells (Vemula et al., 2010; Amengual and Barrett, 2019). Leukocytes can be rapidly activated in vascular inflammation and migrate to the inflammation site (Dong et al., 2017; Chu et al., 2018). The molecules expressed in inflammatory vascular endothelium, such as selectins, ICAM-1, and VCAM-1, significantly promote transendothelial extravasation, adhesion, and recruitment of circulating leukocytes to the vessel wall (Pober and Sessa, 2007; Galvani et al., 2015; Jin et al., 2018). Martinez et al. (2018) studied leukocyte-based biomimetic nanoparticles called lekosomes (Figure 3). The authors assembled leukocyte phospholipids and membrane protein binding into lekosomes, which accumulated in inflammatory vascular lesions fourfold more than controls after administration to mice with atherosclerotic plaques. They also demonstrated that the targeting effect of lekosomes was due to the expression of lymphatic CD45 and function-associated antigen-1 (LFA-1) on the leukocyte membrane. Due to the lipid properties of lekosomes, they can be used as a novel therapeutic agent loaded with therapeutic drugs with different physical properties. Furthermore, Boada et al. used bionic drug carrier lekosomes loaded with rapamycin for atherosclerosis treatment, which could inhibit the proliferation of macrophages in the aorta and slow down atherosclerosis (Boada et al., 2020).

Erythrocytes are considered long-term circulatory transport carriers *in vivo*. Due to their highly hydrophilic properties, the stability of the nanoparticles encapsulated by the erythrocyte membrane can be enhanced with polysaccharides on the erythrocyte membrane surface (Yang L. et al., 2020). As drug

carriers, erythrocytes can prolong the half-life of drugs and reduce adverse reactions and immunogenicity (Luk et al., 2014; Zhang et al., 2017; Alapan et al., 2018). Additionally, erythrocyte membranes express CD47 transmembrane protein, which blocks macrophage uptake by selectively binding to SIRP α expressed by macrophages (Wang et al., 2020b). Thus, nanoparticles disguised by erythrocyte membranes might prolong the time in blood circulation and enhance their levels in the target site. Hu et al. first reported a natural erythrocyte membrane-encapsulated poly (lactic-co-glycolic acid) (PLGA) nanoparticle that significantly prolonged the *in vivo* circulation time compared to only PLGA and PEGylated PLGA (Hu et al., 2011). Studies have also reported that nanoparticles coated with erythrocyte membranes have significant therapeutic effects in treating thrombosis, atherosclerosis, sepsis, and other vascular diseases (Wang Y. et al., 2019; Ben-Akiva et al., 2020; Zhao et al., 2020; Liang et al., 2022).

Besides other proteins such as CD55 and CD59, the platelet membrane surface expresses CD47 to protect them from the absorption of macrophages and enable long-lasting circulation in the vasculature (Hu C. M. et al., 2015; Hu Q. et al., 2015). Studies have demonstrated that P-selectin and CD40 ligands expressed on the surface of erythrocyte membranes can regulate many disease processes, especially inflammation and tumors (Borsig et al., 2001; Sprague et al., 2007). According to the characteristics of aggregation and adhesion and the physiological function of platelets in inflammation, the targeting of atherosclerotic disease has been achieved by platelet membrane-encapsulated nanoparticles (Kunde and Wairkar, 2021). This idea is also supported by the usage of nanoparticles coated with platelet membranes in the imaging of atherosclerotic plaque (Wei et al., 2018). The ability of nanoparticles to interact with Ecs has been used to develop platelet membrane camouflaged nanoparticles to treat atherosclerosis (Wei et al., 2018; Song et al., 2019; Chen L. et al., 2022). For example, Song's team developed platelet membrane-encapsulated PLGA nanoparticles loaded with anti-atherosclerotic rapamycin. The *in vitro* adhesion experiments were analyzed by flow cytometry and fluorescence imaging. These platelet membrane-encapsulated nanoparticles bound 8.34 times more fluorescently to collagen and 9.61 times to fibronectin than the control. Additionally, compared to the control, the biomimetic nanoparticles exhibited significantly high targeting activity *in vivo* to atherosclerotic plaques (4.98 times), indicating the long-lasting circulation and effective adhesion of biomimetic nanoparticles to plaques *in vivo*. After *in vivo* treatment in mice, atherosclerotic plaque lesions in the aorta were significantly reduced by 14.5% \pm 2.9% compared to other nanoparticles and free rapamycin (Song et al., 2019).

Extracellular vesicles (EVs), produced and released by cells such as neutrophils and platelets, can specifically target inflammation and tissue sites (Shah et al., 2018). Gao et al. (2016) designed a DDS based on a nanovesicle with a nanobubble core formed by cell membranes produced by activated neutrophils. The EVs derived from neutrophils could interact with Ecs by binding to the ICAM-1 (Kolaczowska and Kubes, 2013). The EVs derived from platelet are significantly involved in thrombosis. The coagulation activity of these EVs is 50–100 times greater than activated platelets in circulation (Yin et al., 2015). Meanwhile, injecting EVs sourced from platelets through the tail vein in tail-bleeding model mice could

induce hemostasis. Platelet treatment reduced bleeding by 45% compared to controls, while treatment with EVs isolated from platelet decreased bleeding by 62% (Miyazawa et al., 2019).

Cell-derived biomimetic nano-DDS cleverly combine the advantages of nanoparticles and natural biofilms to achieve some remarkable achievements in the treatment of vascular diseases, allowing better biocompatibility, longer *in vivo* circulation time, and targeting of inflammatory sites. However, many challenges remain. For example, compared to ordinary nanoparticles, highly synthetic techniques and complex procedures are required for biomimetic nanoparticle preparation using cell membranes. Maintaining nanoparticles' physicochemical and biological properties during synthesis is crucial (Molinero et al., 2018). Zinger et al. studied the effects of different parameters in the synthesis process of biomimetic nanoparticles on their physicochemistry and biomimetic properties and targeting (Zinger et al., 2021). During the extraction and encapsulation of cell membranes, maintaining the surface biological factors' function and integrity of the cell membrane are important to producing biomimetic nanoparticles on a large scale. Detachment of cell membrane structure or premature drug release during nanomedicine therapy can also lead to reduced targeting and efficacy (Yang L. et al., 2020).

2.3 Physical triggering strategies

The combination of nanoparticles with physical triggering strategies such as ultrasound (US), magnetic fields, and light allows for precise targeting of nanomedicines within the vasculature, improving targeting and controlling drug release. Microbubbles are commonly used clinically as ultrasound contrast agents with a shell composed of lipids, proteins, or polymers and an interior encased in air or perfluorocarbons. Under ultrasound at a certain frequency, microbubbles cavitate; that is, they oscillate, expand, and implode (Weiss et al., 2013). Nanoparticles can also be coated with liquid perfluorocarbon, and the core perfluorocarbon can vaporize to the gas phase upon activation by ultrasonic energy, known as acoustic droplet vaporization (ADV), followed by the nanoparticles growing in size to form microbubbles, which further burst under the action of ultrasound to release the drug locally (Hou et al., 2022). Additionally, ultrasound-irradiated phase-change nanoparticles have great potential for vascular thrombolysis. Jiang et al. (2020) designed an extracorporeal artificial circulation system to simulate thromboembolism in vascular circulation *in vitro*. H₂O₂/PFP phase transition nanoparticles could produce sustained ultrasound-targeted microbubble destruction (UTMD) with a durable cavitation effect and high thrombolytic efficiency. Microbubble targeting to thrombus sites is time-sensitive, and ultrasound-triggered microbubbles do not achieve maximum thrombolytic efficiency. Therefore, nanoparticles that can actively target and bind the thrombus are usually designed to increase the efficiency of ultrasonic thrombolysis (Zhong et al., 2019; Yang A. et al., 2020; Ma et al., 2020; Gao et al., 2021).

Furthermore, exposure of magnetic microbubbles to magnetic fields can synergistically improve the efficiency of ultrasound

thrombolysis and limit long-term exposure (de Saint Victor et al., 2019; Zhang et al., 2019). Enhanced cavitation effects are observed when magnets are placed at thrombus sites. Thus, magnetic nanoparticles (MagNP) comprise a new tool for intravascular targeted drug delivery of nano-DDS. At the same time, as a contrast agent, the superparamagnetic iron oxide nanoparticles can be used to diagnose cardiovascular diseases by magnetic resonance imaging (MRI) (Zhang S. et al., 2020). For example, researchers have designed PHPMR NPs for the non-invasive treatment of atherosclerotic plaque neovascularization. It encapsulates manganese ferrite (MnFe₂O₄), hematoporphyrin monomethyl ether (HMME), and perfluoropentane (PFP), stabilized by a poly (lactic acid-glycolic acid) (PLGA) shell and bound to an anti-VEGFR-2 antibody. MRI, photoacoustic, and ultrasound imaging were performed. PHPMR NP-mediated sonodynamic therapy (SDT) inhibited neovascularization by generating reactive oxygen species (ROS) to promote apoptosis (Yao et al., 2021). Vascular visualization is important in the diagnosis and treatment of cardiovascular diseases. Researchers have recently developed a carbon nanotube imaging system in which macrophages and monocytes can absorb nanoparticles in atherosclerosis, and photoacoustic imaging *in vitro* can accurately locate and visualize plaques, providing a new approach to the clinical diagnosis of relevant cardiovascular diseases (Gifani et al., 2021). Although researchers have conducted various studies on magnetic DDS, their clinical application remains limited because of the safety of magnetic nanoparticles and because there is no clinically approved medical device to apply a magnetic field to nanoparticles in blood vessels (Sun et al., 2020; Zenych et al., 2020).

3 Extravascular targeting nanoparticles

Additionally, to target intravascular diseases through blood vessels, nanoparticles can target tumor and inflammatory tissues across the vascular endothelium by their enhanced permeability and retention (EPR) effect or neurological diseases by crossing the blood-brain barrier (BBB). Besides intravenous nanoparticles, they can be administered by inhalation and oral and topical administration.

3.1 Binding targets across the vascular endothelium

3.1.1 EPR

Tumor overgrowth results in neovascularization with unusually wide fenestrations and dysplasia of lymphatic vessels in solid tumors, allowing preferential accumulation of nanoparticles in tumors, a phenomenon known as the EPR effect (Maeda et al., 2013; Nakamura et al., 2016), which Matsumura and Maeda first proposed in 1986 (Matsumura and Maeda, 1986). Besides tumors, the EPR effect is used in diseases such as infection, inflammation, and atherosclerosis (Gao et al., 2019; Clausen et al., 2020; Tu et al., 2022). EPR effects are frequently observed in the vascular and tumor sites of inflamed tissues. In general, nanoparticles of 20–200 nm diameter are best suited for passive targeting of drugs to inflamed tissue (Lundy et al., 2016). A recent study in rheumatoid arthritis

TABLE 2 Nanoparticles designed for different components of the tumor microenvironment.

Target site	Nanosystem	Molecular markers	References
Tumor cells	Dox/F127&P123-Tf	Tf	Soe et al. (2019)
	FDMCA	Folic acid	He et al. (2020)
	⁶⁴ Cu-Labeled GE11-Modified Polymeric Micellar NPs	Peptide GE11	Paiva et al. (2020)
	TLS11a-LB@TATp-MSN/DOX	TATp, TLS11a-LB	Ding et al. (2020)
	d-SN38@NPs/iRGD	iRGD	Lin et al. (2020)
	iRGD-PSS@PBAE@JQ1/ORI NPs	iRGD- pss	Chen B. et al. (2022)
	KLAK-MCP-1 micelles	MCP-1 peptide, KLAKLAK peptide	Trac et al. (2021)
ECM in the TME	PM@CDDP/SNP		Chen L. et al. (2021)
	Col-TNPs	Collagenase	Wang et al. (2022)
	HA-sPLGA XNPs	Hyaluronic acid	Wang X. et al. (2021)
Enzymes in the TME	FRRG-DOX NPs	Cathepsin B-cleavable peptide	Shim et al. (2019)
	HEKMs	EGFR-HER2, FRET	Wang Z. et al. (2019)
	PLP-D-R	Antiplatelet antibody R300	Li S. et al. (2017)
	siFAK + CRISPR-PD-L1-LNPs	FAK siRNA	Zhang D. et al. (2022)
	AuNPs-D&H-R&C	RVRRCCK, CABT	Xie et al. (2021)

(RA) showed that 100 nm-sized egg yolk lecithin (EPC) liposomes circulate in mice for up to 12.85 h. The longer the circulation time, the more they accumulate in the inflamed joints (Ren et al., 2019). Endocytosis of nanoparticles by immune cells can be influenced by the shape and surface charge of the nanoparticles (Tu et al., 2022). In this section, we focused on applying EPR effects in tumors. Understanding the EPR effect provided a basis for developing anti-tumor macromolecular drugs and brought hope to nanomedicine. Therapeutic agents, such as gemcitabine, cisplatin, or doxorubicin, are low molecular weight drugs (typically less than 1000 Da) with poor pharmacokinetics and biodistribution (de Jonge and Verweij, 2006). Advances in nanotechnology have led to the development of many DDS, improving the accumulation of agents for chemotherapy at target sites and their biodistribution. By increasing the size of systemically administered drugs to a diameter of about 100 nm, renal excretion can be reduced (considering a renal clearance threshold of about 40,000 Da), blood half-life can be prolonged, and its accumulation in target tissues can be improved (Golombek et al., 2018).

Anti-tumor nanomedicines, including Doxil, Marqibo, and Abraxane, have been successfully used in clinical practice (Jain and Stylianopoulos, 2010; Barenholz, 2012; Silverman and Deitcher, 2013). These nanomedicines use the EPR effect to improve the pharmacokinetics of chemotherapeutic drugs and reduce systemic side effects. Encapsulation of doxorubicin into liposomes (Doxil) increases the plasma half-life of the free drug from 5 to 10 min to 2–3 days (Gabizon et al., 1994). Doxil, the first FDA-approved nanomedicine, has 100 nm and uses the stealthy polymer polyethylene glycol (PEG) for surface modification to reduce the aggregation and opsonization of plasma proteins, extending its circulating half-life in the blood (Barenholz, 2012;

Suk et al., 2016). Doxil leads to 4–16 times higher drug concentrations in malignant effusions than free doxorubicin, a phenomenon demonstrating the EPR effect. Meanwhile, Doxil has been approved for treating ovarian cancer, breast cancer, and multiple myeloma, among other diseases (Min et al., 2015). However, the nanomedicines mentioned above are not good enough to prolong patient survival because nanoparticle delivery using the EPR effect is also hampered by the tumor microenvironment, such as the stromal compartment composed of extracellular matrix (ECM) and mesenchymal cells, interstitial fluid pressure (IFP), and poor blood flow. Collagen, fibronectin, and hyaluronic acid in the ECM form a barrier outside tumor cells that promotes tumor growth, prevents nanodrugs from penetrating deeply into the tumor mesenchyme from blood vessels, and strongly affects the accumulation of nanodrugs in tumors (Yokoi et al., 2014; Nissen et al., 2019). Due to the increased permeability of tumor blood vessels, leakage of substances from the plasma through the blood vessels leads to increased interstitial fluid pressure and the lack of a normal lymphatic drainage system, creating high interstitial fluid pressure impairs the penetration and accumulation of nanodrugs (Gao X. et al., 2017; Glicksman et al., 2017). Previous studies have demonstrated the effects of interstitial fluid pressure on tumor size using tumor models (Ruan et al., 2018). Due to the specificity of tumor neovascularization, blood vessels have impaired perfusion and slow blood flow compared to normal tissues (Hori et al., 2000). However, with the in-depth study of the EPR effect, scientists have increasingly recognized its high heterogeneity. One reason for this is the variability between experimental mouse models and patients. Also, tumors of the same origin vary across patients or periods (Tanaka et al., 2017; Fang et al., 2020).

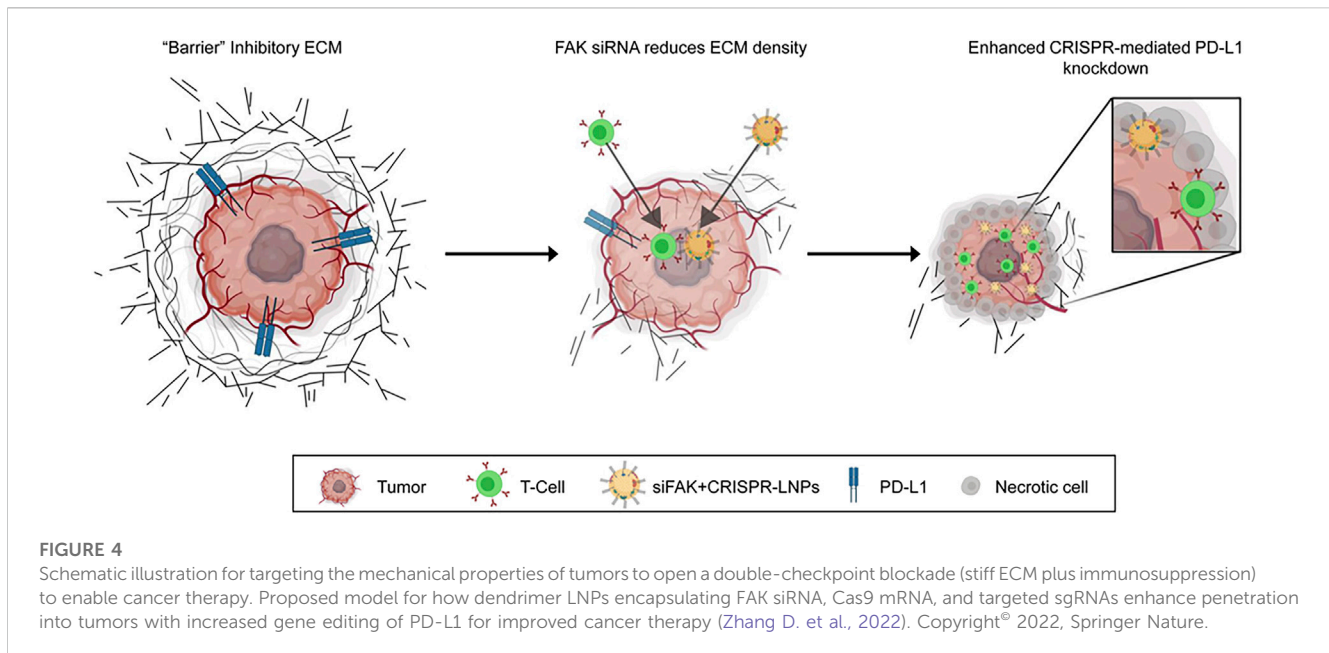
In summary, the EPR effect alone cannot effectively and completely eliminate tumor cells using nanomedicines. Therefore, modification of the nanoparticle surface with molecular markers and external physical stimuli might be effective “EPR enhancers.” Next, we discuss the mechanisms and research progress of these two emerging strategies.

3.1.1.1 EPR combined with molecular markers enables nanoparticle targeting

Modifying nanoparticles using molecular markers can enhance the active targeting ability of nanoparticles, increase cytotoxicity against tumors and reduce systemic side effects (Table 2). In other words, nanoparticle interactions with target cell surface molecules, such as ligand-receptor, enzyme-substrate or antibody-antigen-mediated interactions, are utilized (Nag and Delehanty, 2019). Many targets are overexpressed in tumor cells, making them potential targets for nanoparticles. Transferrin receptors are overexpressed on the surface of most tumor cells. Conversely, they are underexpressed in normal cells. Moreover, transferrin-modified nanoparticles can enhance drug delivery efficiency in tumor cells (Soe et al., 2019; Bellini et al., 2020). Transferrin-based nanotherapeutic probes have also been developed to achieve early tumor diagnosis through active targeting (Jiang et al., 2022). Widespread upregulation of folate receptor expression in many cancers has also been demonstrated, making it an ideal target for nanomedicines (Wang et al., 2020a; He et al., 2020; Scaranti et al., 2020). Additionally, the epidermal growth factor receptor (EGFR), which belongs to the ErbB family of receptor tyrosine kinases, is overexpressed in various human cancers, becoming a target for cancer therapies even used in clinical treatment (Sigismund et al., 2018). In a recent study, modification of the surface of the nanoparticles with peptide GE11 was performed to deliver the anti-tumor drugs to tumor sites in a colorectal cancer mouse model. The *in vitro* fluorescence results showed significantly enhanced internalization of the treatment nanoparticles on EGFR-expressing HCT116 colon cancer cells compared to controls (Paiva et al., 2020). Furthermore, Ding et al. (2020) designed the TLS11a-LB@TATp-MSN/DOX nanoparticle, specifically targeting H22 cells using the nuclear localization signal peptide TATp and the aptamer TLS11 as modified nanoparticles. The *in vivo* experiments with tumor-bearing mice demonstrated that the nanoparticles could enrich and target chemotherapeutic drug delivery to the nucleus of hepatocellular carcinoma cells in liver cancer tissues. Nanoparticles can also bind tumor-penetrating peptides (TPPs) on their surface, specifically binding to receptors expressed on tumor endothelial cells and performing transendothelial transport pathways to extravasate nanoparticles from tumor blood actively (Liu et al., 2017). As a peptide with tumor penetrating activity, iRGD (CRGDK/RGPD/EC) can be used for the surface modification of nanoparticles. Many experimental studies on iRGD have confirmed that its modification in iRGD can improve the targeting and retention of nanoparticles in tumors (Lin et al., 2020; Li H. et al., 2021; Chen B. et al., 2022). Immune cells in the tumor microenvironment (TME) also influence the aggregation of nanoparticles. For example, tumor-associated macrophages (TAMs) are key to tumor growth (Mantovani et al., 2017), and targeting macrophages as nanoparticles can be a therapeutic

strategy. Two recent studies have successfully inhibited the recruitment of TAMs to tumors by specifically targeting CCR2 on macrophages (Zhang X. et al., 2021; Trac et al., 2021). The uptake of nanoparticles by cells is via phagocytic or non-phagocytic pathways, such as clathrin and caveolae-mediated endocytosis, resulting in transendothelial and transcellular transport and relatively uniform distribution throughout the tumor (Li Z. et al., 2017; Zhou et al., 2019). Transcytosis is an important active transport process in which biomacromolecules are transported through dense epithelial and endothelial cells. During transcytosis, biomacromolecules are internalized by cells and excreted from the body (Niu et al., 2021). Transcytosis has been proven to be an effective approach to improve the penetration of nanoparticles into tumors (Wang et al., 2022).

Besides targeting tumor cells, improving the complex ECM in the TME is a prominent strategy to enhance the penetration and retention of nanoparticles in the tumor ECM (Uthaman et al., 2018). The ECM is inextricably linked to tumor cell development, metastasis, and invasion. Key ECM components, such as hyaluronic acid and collagen, form a dense biological barrier that prevents nanomedicines from penetrating deep into tumor cells, resulting in uneven drug delivery (Poltavets et al., 2018; Guo et al., 2021). Many studies have been reported using new materials and strategies to facilitate the penetration of nanomedicines into the ECM. A tumor-specific ONOO⁻ nanogenerator (PM@CDDP/SNP, abbreviated as PMCS) was designed to produce ONOO⁻ and more matrix metalloproteinases in a specific TME, and degrade its dense ECM, enhancing the EPR effect and promoting drug penetration and accumulation deep in the tumor (Chen Y. et al., 2021). Wang et al. (2022) designed nanoparticles modified with collagenase and demonstrated that the endocytosis of nanoparticles could be effectively increased by degrading collagen, indicating that the dense fibrous collagen prevented the penetration of nanomolecules and chemotherapeutic drugs into tumors. Hyaluronic acid binds to the CD44 receptor, upregulated in various cancer cells, which improves ECM targeting and has good therapeutic potential in some cancers (Liu et al., 2018; Choi et al., 2019; Wang X. et al., 2021). Studies targeting hyaluronic acid-modified nanoparticles are important for further nanomedicine development. For example, Wang et al. used fluorescence imaging and showed that DTX-HA-sPLGA XNPs rapidly potentiated aggregation in tumors and extended the elimination half-life to 4.18 h, 18.2 times the free DTX after 8 h of injection in mice (Wang X. et al., 2021). There are also studies using hyaluronidase to eliminate hyaluronic acid from ECM and a phase III clinical trial with pancreatic cancer patients in 2018 (Doherty et al., 2018; Infante et al., 2018). Besides hyaluronidase and collagenase, other enzymes can degrade the ECM. Higashi et al. (2020) prepared PEG pineapple enzyme to study its therapeutic potential in pancreatic cancer. After PEG intravenous injection, bromelain can significantly accumulate in the tumor through the EPR effect and exhibit a strong ability to degrade the ECM. Therefore, reducing the tumor ECM can enhance the penetration of nanodrugs and increase the intra-tumor drug concentration. Furthermore, it has been shown that the degradation of collagen, a key component of ECM, effectively enhances the intracellular transcytosis of nanoparticles (Wang et al., 2022). Recently, researchers have explored the interaction characteristics between



nanomedicines and the ECM. Cheng et al. first found that nanoparticles bind tightly to specific lipid components in the ECM, namely, retraction fibers (RFs) and migration, to inhibit cell migration. This interaction provides a potential therapeutic target and strategy for nanomedicines against tumor metastasis (Cheng et al., 2022).

Several specific enzymes in the TME, such as histone B, matrix metalloproteinases, and caspase, can enhance the targeting of nanodrugs and improve therapeutic efficacy (Abumanhal-Masarweh et al., 2019; Shim et al., 2019; Wang Z. et al., 2019). A research team has developed a novel drug delivery system targeting tumor vasculature, a polymer-lipid-peptide-based (PLP) DDS. The PLP was constructed using two portions: a polymeric core nanoparticle and a shell layer. The core nanoparticle was constructed with the biodegradable and biocompatible block copolymer poly (etherimide)-poly (lactic-co-glycolic acid)2 (PEI-(PLGA)2) and loaded with the chemotherapeutic agent DOX and antiplatelet antibody R300. The shell layer contained PEGylated phospholipids, lecithins, and matrix metalloproteinase 2 (MMP2)-cleavable peptides. R300 is specifically released in the tumor on the cleavage of the lipid-peptide shell of the nanoparticles by MMP2, which is commonly overexpressed in tumor vascular endothelia and stroma. R300 induces tumor vascular damage and disrupts the tumor vascular barrier by depleting intra-tumor platelets and promoting massive neutrophil infiltration (Gros et al., 2015; Hillgruber et al., 2015). This treatment can effectively improve tumor vascular permeability, increase the accumulation of drug particles in tumors, promote tumor regression, and inhibit tumor metastasis (Li S. et al., 2017). Additionally, focal adhesion kinase (FAK) activation is related to the generation of ECM stiffness (Seong et al., 2013). Inhibition of FAK activity also enhances the infiltration of CD8⁺ cytotoxic T cells (Serrels et al., 2015; Jiang et al., 2016). For example, Zhang et al. designed a self-assembled nanoparticle LNPs (siFAK + CRISPR-LNPs) targeting FAK in tumor tissues to improve the mechanical

characteristics of ECM, enhance drug penetration, and effectively inhibit the growth of cancer cells (Figure 4) (Zhang D. et al., 2022). Also, proprotein convertase furin is a specific target for breast cancer diagnosis and treatment, as it is highly expressed in breast cancer (Jaaks and Bernasconi, 2017; Li et al., 2019; Zhu et al., 2019). A recent study has designed a furin-responsive aggregated nanoplatform to improve drug delivery efficiency (Xie et al., 2021).

3.1.1.2 EPR combined with physical stimulation enables nanoparticle targeting

The ability of nanoparticles to penetrate tumor tissue can be enhanced using physical stimulation. External physical stimulation by laser, ultrasound, radiation, and electric fields can alter the TME and improve the penetration effect of nanomaterials within the tumor.

Radiotherapy (RT) is one of the current clinical treatments for solid tumors, either as monotherapy or combined. RT destroys tumor cells and TME by generating energy and ROS through external radiation exposure but can have some effect on healthy tissue cells (Boateng and Ngwa, 2019). Because of the enhanced expression of vasoactive mediators (e.g., VEGF), induced apoptosis of endothelial cells, and increased tumor vascular permeability, RT can increase the accumulation of nanodrugs in tumor tissues (Ojha et al., 2017). Yang et al. developed a multi-functional theranostic system based on poly acrylic acid-coated ultra-small superparamagnetic iron oxide nanoparticles (PAA@USPIOs), GE11-PDA-Pt@USPIOs. This system was conjugated with GE11 peptide, coated with polydopamine, and loaded with cisplatin. After intravenous injection of nanoparticles, MRI and PA imaging showed that GE11-PDA-Pt@USPIOs efficiently accumulated in tumors. The use of RT further enhanced the antitumor efficacy of chemotherapeutic agents (Yang et al., 2019). Meanwhile, Charest et al. developed a novel nanocomplex by wrapping carboplatin and gold nanoparticles into a liposomal formulation. The dosage of gold nanomaterials and carboplatin

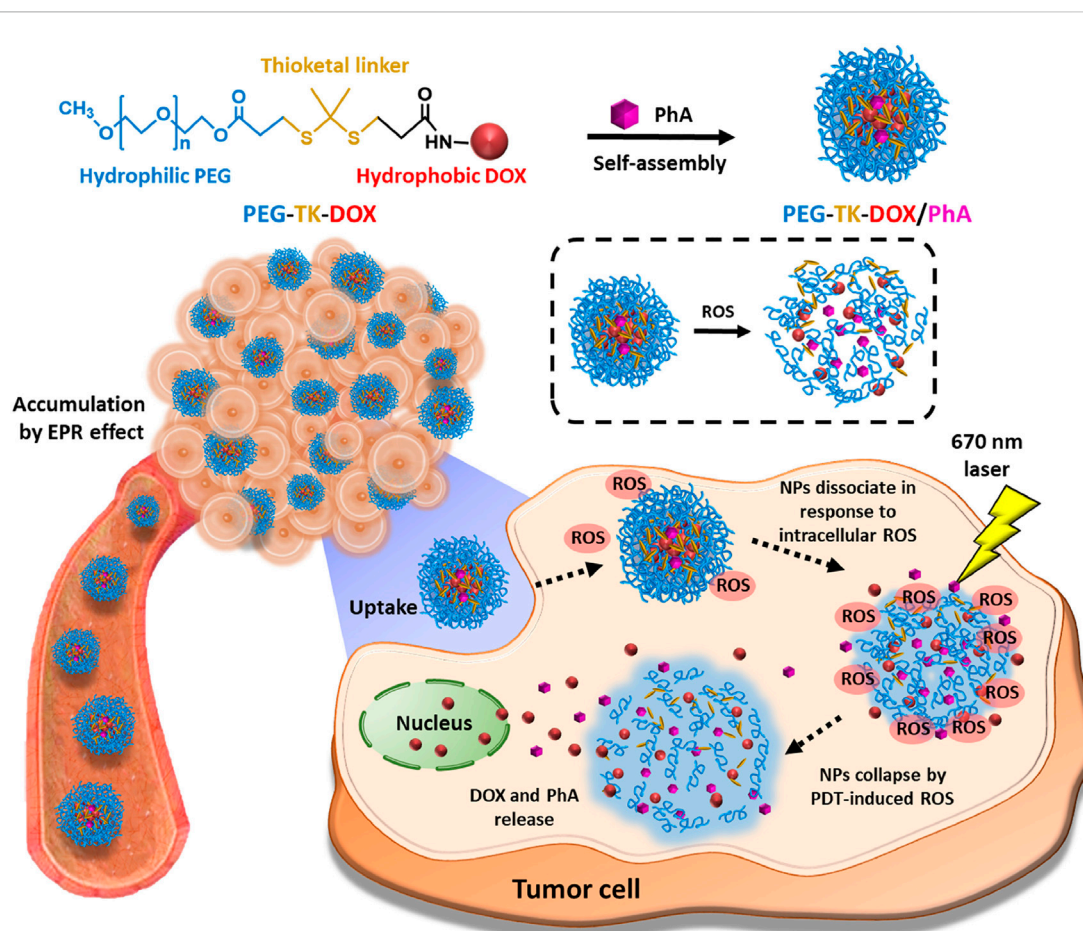


FIGURE 5

Schematic diagram of the mechanism underlying the action of PEG-TK-DOX/PhA (Kim et al., 2020). Copyright© 2020, Elsevier.

equipped in liposomal nanomaterials was the same. The *in vitro* application of RT for combination therapy significantly inhibited tumor growth (Charest et al., 2020). As an adjunct to cancer treatment, heat therapy (HT) has a synergistic effect on chemotherapy and radiotherapy (Dunne et al., 2020). Local hyperthermia of tissues can increase blood flow, change vascular permeability, and promote drug aggregation at the tumor site. Effective synergistic killing of tumor cells by magnetic hyperthermia therapy in combination with chemotherapy has been documented (Song et al., 2020).

Light is a form of electromagnetic radiation and can be used as a physical trigger strategy. Ultraviolet and visible lights have a shallow penetration depth due to their shorter wavelengths. The opposite is true for near-infrared light. Using light and photosensitizers, two physical triggering strategies, photothermal therapy (PTT), and photodynamic therapy (PDT), can potentially enhance the EPR effect. PDT generates ROS using photosensitizers in combination with specific light wavelengths, leading to cell death (Dhaliwal and Zheng, 2019). PDT induces increased vascular permeability at the tumor site and can improve the EPR effect of nanoparticles after administration (Hare et al., 2017). PDT is a non-invasive treatment, and nanoparticles have been increasingly used for PDT with efficient targeting of tumors (Kim et al., 2020; Paris et al., 2020). Due to the

tumor hypoxic microenvironment, many studies have developed nanocarriers capable of performing self-oxygenation to increase the therapeutic efficiency of PDT (Huang et al., 2019; Liu et al., 2020). Kim et al. (2020) developed an adriamycin and photosensitizers-encapsulated nanoparticle system that could effectively respond to ROS (Figure 5). Based on the EPR effect, nanoparticles accumulate in tumors, and endogenous ROS and ROS generated during PDT prompt the nanoparticles to release adriamycin and photosensitizers, and produce more ROS to make nanoparticles accumulate. PTT is a new non-invasive treatment method that uses photothermal agents (PAs) to convert light into heat to kill cells when irradiated by an external light source such as near-infrared light (Zhi et al., 2020). One study reported a novel small molecule NIR-IIb dye IT-TQF with a D-A-D structure encapsulated into DSPE-PEG₂₀₀₀ to construct IT-TQF NPs. IT-TQF NPs have good photostability, and their high therapeutic potential for tumor PTT was demonstrated *in vitro* and *in vivo* with photothermal performance tests. The *in vivo* photothermal treatment was performed on a 143B subcutaneous tumor mouse model after intravenous injection of IT-TQF NPs. The tumors were successfully suppressed after photothermal treatment in the IT-TQF NPs combined with the laser treatment group, demonstrating the good photothermal treatment effect of IT-TQF NPs *in vivo* (Lou

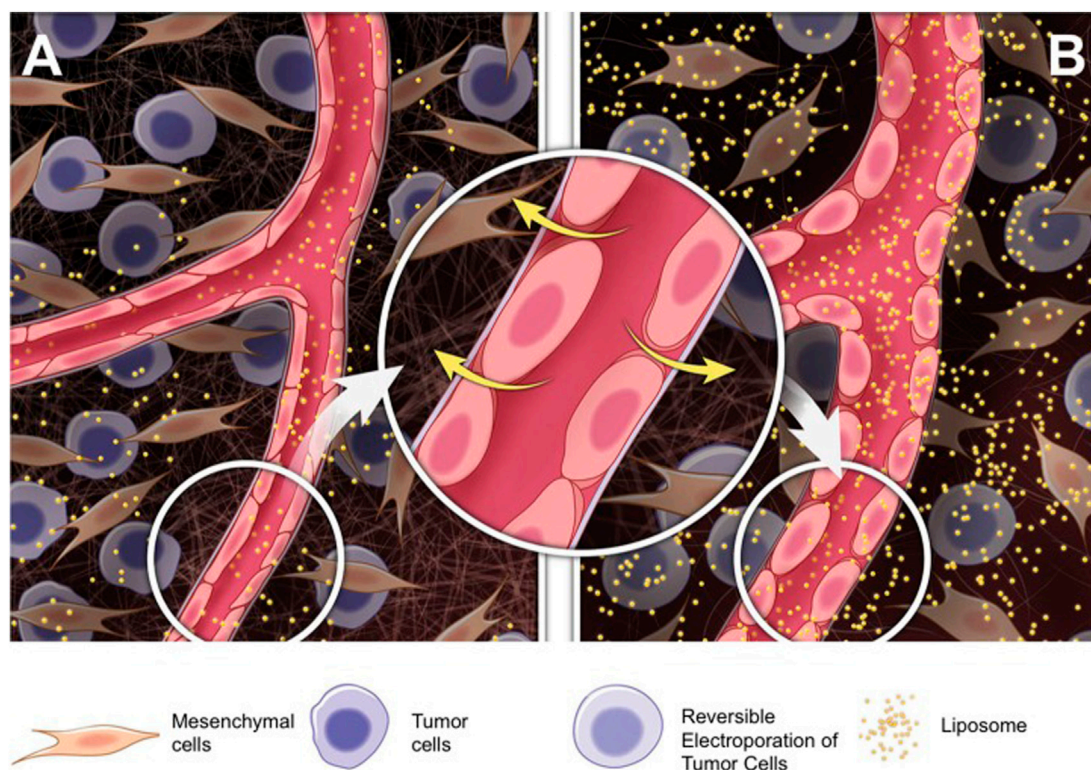


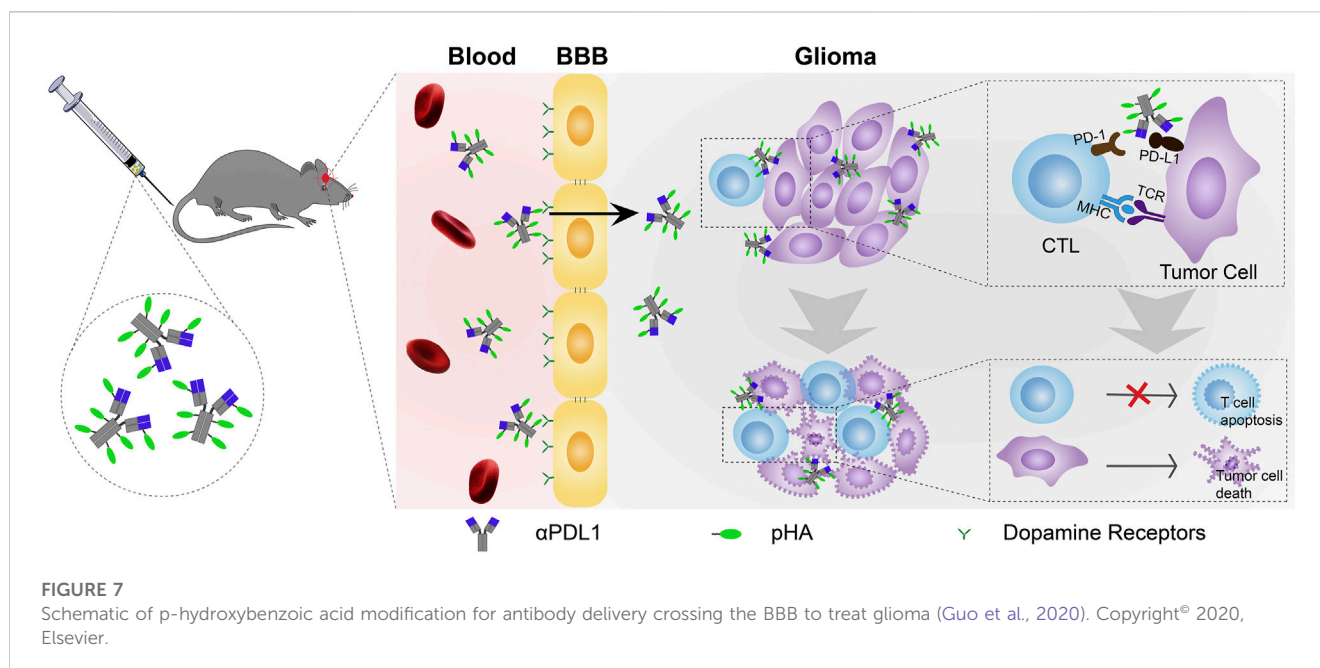
FIGURE 6

Mechanisms underlying the promotion of RE-associated vascular effects on liposomal nanoparticle delivery. Compared to (A) Untreated tumors, (B) RE induces rounding of endothelial cells and penetration of nanoparticles into treated tumors. RE, reversible electroporation (Srimathveeravalli et al., 2018). Copyright © 2018, SAGE.

et al., 2022). However, one limitation of PDT/PTT is that light does not penetrate deep enough into the tissue to allow radical treatment of deep tumors. Therefore, there is an urgent need to develop treatments that can effectively compensate for the shortcomings of PDT/PTT.

Furthermore, ultrasound can significantly promote the EPR effect by enhancing cell membrane permeability. Ultrasound is of great interest due to its easy operation, non-invasive nature, and high tissue penetration depth (Duan et al., 2020). Acoustic perforation comprises the expansion and bursting of gas-filled microbubbles under ultrasound irradiation, which physically disrupts blood vessels to facilitate drug delivery (Duan et al., 2020). Combining the use of ultrasound and therapeutic microbubbles can enhance the EPR effect. For example, Koczera et al. loaded different drug types and targeted poly (n-butyl cyanoacrylate) (PBCA) microbubbles for imaging and drug delivery. Combining the microbubbles with ultrasound allowed the effective passage of drugs through the vessel wall (Koczera et al., 2017). Another study described an ultrasound-mediated liposome nanoparticle-based DDS, in which ultrasound improved nanoparticle accumulation in tumor tissue by increasing penetration of liposomes from the vasculature into the ECM. Tumor sizes were reduced, and survival was prolonged in mice (Olsman et al., 2020). Additionally, pHIFU can disrupt and remodel the collagen and hyaluronic acid network in the ECM without causing

changes in vessel size and structure (Wang et al., 2012). Several teams have investigated the use of pulsed HIFU (pHIFU) to improve the tumor targeting efficiency and the tissue penetration of nanoparticles (Lee et al., 2017; You et al., 2017). For example, You et al. (2017) injected glycol chitosan nanoparticles (FCNPs) modified with fluorescent dyes into the femoral vein of mice. The pHIFU enhanced tissue penetration and nanoparticle extravasation in mouse femoral tissue under the following treatment conditions: frequency: 1.5 MHz, duty cycle: 10%, pulse repetition frequency: 1 Hz, time: 30 s, and interval: 2 mm. However, along with the increasing treatment power, hyperthermia might be induced by the pHIFU in the target tissue, leading to histopathological abnormalities in the target tissue. Additionally, excessive pHIFU treatment might result in irreversible tissue damage and reduce the permeability of nanoparticles into tissues. Therefore, optimizing the therapeutic dose of pHIFU is particularly important in applying these pHIFU strategies for drug delivery in clinics. Hyperthermia of tissues by US action might also further dilate blood vessels and increase blood perfusion to promote the EPR effect. Fu et al. (2021) provided a therapeutic strategy to induce iron death and apoptosis in tumor cells by creating hyperthermic conditions with nanoparticles loaded with ferrate and doxorubicin combined with US. Because of the EPR effect, nanoparticles could accumulate in the tumor, and HT effectively stimulated the co-release of doxorubicin and ferrate



in the tumor tissues. After 1-h US and nanoparticle treatment, tumor oxyhemoglobin saturation was enhanced from 15.4% to 36.0%. The tumor volume of mice significantly reduced after more than 15 days of treatment with nanoparticles and US.

Electroporation (EP) has recently been studied as an “EPR effect enhancer.” Certain electric fields can cause reversible structural changes in the cell membrane, known as electroporation (Djokic et al., 2018). Besides affecting the permeability of cell membranes, electrical impulses also improve vascular permeability (Srimathveeravalli et al., 2018). Srimathveeravalli et al. (2018) studied a liposome nanoparticle (89Zr-NRep) and showed that altered vascular permeability due to EP after administration via the intravenous route might be another mode of nanoparticle entry into tumors (Figure 6). They also found that tumor absorption of nanoparticles between pre- and post-EP injections did not differ within 24 h, indicating that the vascular effect caused by EP can promote nanoparticle deposition to the tumor for some time after membrane permeability is restored. Based on the above phenomenon, they hypothesized that the vascular effect associated with reversible electroporation could improve the EPR effect and play an important role in the delivery of nanoparticles to tumors. Kodama et al. (2019) also investigated the effects of EP on tumor vasculature and the TME. They demonstrated the ability of EP to promote the aggregation of nanoparticles toward the tumor and improve the therapeutic effects. Nevertheless, the relationship between EP and EPR effects needs further investigation.

3.1.2 BBB

As a microvascular network, the BBB is constructed by supporting cellular structures and brain endothelial cells, such as neurons, possibly immune cells, pericytes, and the endfeet of astrocytes. The BBB can effectively separate the central nervous system from the peripheral blood circulation (Daneman and Prat, 2015). The integrity of the BBB is critical to maintaining normal neurological function and brain homeostasis. However, most drugs

used to treat brain disorders cannot cross the BBB in sufficient doses to the diseased brain tissues and cells. Therefore, there is an urgent need to develop drug delivery systems that can penetrate the BBB and deliver the drug to brain tissues. Nanoparticles are potential candidates as brain-targeted drug carriers. Nanoparticles are smaller, have lower toxicity and controlled drug-release properties, and are easily modified with proteins that target specific receptors on their surface. Nanoparticle-based DDS can cross the BBB more effectively and deliver drugs to the target site (Ahlawat et al., 2020). Nanoparticles have to be absorbed by the endothelial cells of the BBB for exocytosis to the other side with receptor-mediated endocytosis to reach the central nervous system. It has been shown that tight junctions in the endothelium of the central nervous system are opened during neuroinflammation, enhancing the transcytosis of the BBB, which allows uptake of nanoparticles (Villaseñor et al., 2019).

Nanoparticles can cross the endothelium by endocytosis and exocytosis. Transcytosis is divided into receptor-mediated transcytosis, which involves ligands, and adsorptive transcytosis, which can be used for cationic nanoparticles (Pandit et al., 2020). Nanoparticle surfaces can bind to specific ligands, such as proteins, peptides, and antibodies that specifically bind to the receptors highly expressed on the cell surface or even alone on the endothelial cells of the brain (Zhang W. et al., 2021). These ligands, often referred to as “Trojan horses,” are recognized and internalized by the transporter system on the BBB along with the associated nanoparticles to enter the brain (Choudhari et al., 2021). Commonly used receptor-ligand pairs for drug delivery to the brain include angiopep-2/LRP1, glucose/glucose transporter protein GLUT1, and transferrin/transferrin receptor (Galstyan et al., 2019). The transferrin receptor is overexpressed on brain endothelial cells and transports transferrin across the endothelium via receptor-mediated endocytosis (RMT). Transferrin/transferrin receptors have been extensively studied to increase the delivery of therapeutic agents to the brain (Johnsen et al., 2017; Fan et al.,

2018). Glucose is a major energy source in the brain and is transported by the glucose transporter protein GLUT1, present in relatively high densities in BBB endothelial cells to guarantee an adequate energy supply to the brain. Fasting and the elevation of blood glucose can effectively enhance GLUT1 expression, leading to dramatically increased transportation of glucose-fixed nanoparticles across the BBB (Anraku et al., 2017). Due to the high expression in glioblastoma and BBB vascular endothelial cells, angiopep-2/LRP1 focus on glioblastoma treatment and therapy (Zhu et al., 2022). LRP1 targeted treatment can directly penetrate the BBB and deliver the drugs into brain tumor cells. Para-hydroxybenzoic acid can target dopamine receptors and promote BBB penetration via RMT. Nanoparticles modified with para-hydroxybenzoic acid could deliver PD-L1 antibody (α -PDL1), an immune checkpoint inhibitor that cannot penetrate the BBB, to the surface of glioma cells and more effectively reduce the growth of tumor cells in a glioblastoma mouse model (Figure 7) (Guo et al., 2020). The interaction of nanoparticle surface properties with the plasma membrane of endothelial cells can also be exploited for adsorption-mediated cytotaxis (AMT) into the BBB. Modifying cationic charges and conjugated compounds on nanoparticles, including heparin, cardiolipin, and lectins, can pass through the BBB (Pinheiro et al., 2021).

However, using these natural ligands, such as transferrin, glucose, insulin, leptin, or other receptor-related proteins, has limitations since they can compete with endogenous ligands, making it impossible to capture the concentration of the drug being administered (Li J. et al., 2021). The solution usually uses antibodies or peptides in place of or combination with natural ligands. For example, it is difficult to deliver sufficient drug doses to glioma patients via Angiopep-2/LRP1 administration alone due to receptor saturation effects. Moreover, combining a cell-penetrating peptide, the trans-activator of transcription (TAT) peptide, with Angiopep-2 can enhance the concentration of the drug reaching the tumor site (Zhu et al., 2022). Another study using anti-TfR/BACE1 antibody significantly improved the BBB targeting of AuNPs without interfering with endogenous transferrin (Johnsen et al., 2018). Using physical methods to reversibly open the BBB can also facilitate the nanoparticle transport of drugs to the brain. Many physical methods have been studied, such as US, magnetic fields, and light (Tabatabaei et al., 2015; Zhang D. Y. et al., 2020; Li X. et al., 2021). Focused ultrasound (FUS) binds to intravascular microbubbles to increase BBB permeability by opening tight junctions and creating endothelial cell openings. Olsman et al. showed that combining FUS and microbubbles with transferrin receptor-targeting liposomes increases drug delivery to the brain compared to liposomes lacking BBB targeting (Olsman et al., 2021). Parameters such as pulse length and frequency should also be considered when using FUS (Lapin et al., 2020).

The transcytosis of nanoparticles by the cells is influenced by the physicochemical characteristics of the nanoparticles (e.g., size, shape and surface chemistry) as well as the experimental conditions employed (Salatin and Yari Khosroushahi, 2017). The key factors controlling BBB transport efficiency are the total ligand avidity and density on nanoparticles. Increasing the ligand density increases the affinity for the receptor, increasing the likelihood of endothelial cell internalization (Johnsen et al., 2019). However, too high densities can lead to spatial site block, reduced diffusion coefficients, and

increased size of nanoparticles. Intracellular transport patterns, such as the endocytosis mediated by clathrin, also vary according to the density of the ligand (Alkilany et al., 2019). Moreover, a too-high ligand density might lead to the inability of nanoparticles to be released from the cell surface across the BBB due to high affinity (Deng et al., 2019). Therefore, the optimal ligand density is that the ligand can provide sufficient affinity for the interaction, and this interaction is compromised. For example, compared to the surface density of 10 or 50, 25% surface glucose exhibits the best BBB permeability by recognizing GLUT1 on endothelial cells (Anraku et al., 2017). Johnsen et al. also investigated the effects of TfR antibody density on the uptake and transport of nanoparticles into the brain (Johnsen et al., 2019). Safety is another issue when using these receptors for human brain-targeted delivery. For example, TfR and GLUT1 are not exclusively expressed in brain endothelial cells, implying that brain-targeting strategies might increase drug uptake in peripheral tissues (Couch et al., 2013). Therefore, targets with high expression in the BBB and low expression in other tissues must be found to improve the safety of CNS disease treatments effectively. The efficiency of TfR-targeted delivery technologies might also vary depending on the differences between species. For example, a proteomics study showed that TfR levels in mouse brain microvasculature were approximately 2.5-fold higher than in human brain microvasculature. This difference in TfR levels must be considered when we extrapolate animal data to humans (Terstappen et al., 2021).

3.2 Extravascular administration target binding

Besides intravenously binding to vascular targets or crossing the endothelium to reach extravascular tissues, nanoparticles can also deliver drugs through oral, inhalation, and topical administration (e.g., transdermal, intraperitoneal) without passing intravascular targets.

3.2.1 Oral administration

The oral route is the most convenient, practical, and preferred administration strategy because most drugs are currently administered orally, and most patients prefer oral to intravenous administration. However, absorbing oral drugs requires overcoming some physiological barriers in the gastrointestinal tract. Nanodrug delivery platforms can transport malabsorbed drugs to the gastrointestinal tract and improve oral bioavailability. Coating nanoparticles with biological mucus modify their surface properties and increases the mucosal diffusion rate, gastrointestinal retention time, and systemic absorption (Azagury et al., 2022). Modifying ligands on the surface of nanoparticles can also specifically target the gastrointestinal tract. Azevedo et al. used genetic engineering to construct functionalized recombinant albumin with targeted modification on the surface of PLGA-PEG nanoparticles to improve nanoparticle transport across the intestinal epithelium by enhancing the binding between nanoparticles and intestinal neonatal Fc receptors (FcRn) (Azevedo et al., 2020). The delivery of peptides/proteins readily degraded by the gastrointestinal tract via nanoparticles provides an alternative management measure for diabetic patients. Furthermore, Zhou et al. designed a PH-

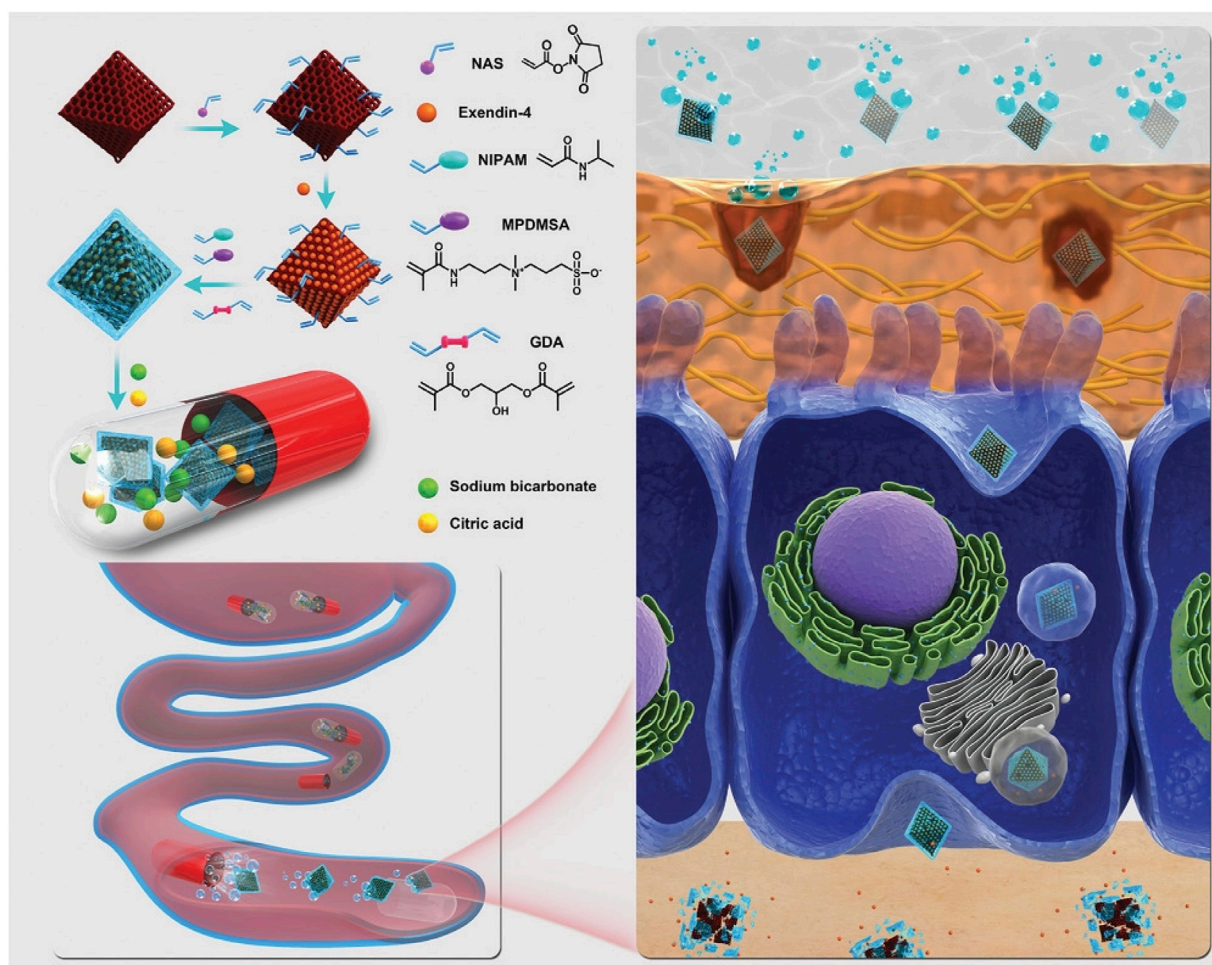


FIGURE 8

Illustration of pH-triggered self-unpacking capsule containing Ex@MIL101@Gel nanoparticles for oral Exendin-4 delivery. The hydrogel-coated MOF nanoparticles containing Exendin-4 were obtained by free radical copolymerization of acryloyl-modified NH₂-MIL101 nanoparticles, NIPAM, and MPDMSA, with GDA as a crosslinker. The capsules protect the peptide-loaded nanoparticles from the stomach's acidic environment and unpack them in the intestine, generating CO₂ bubbles to promote the movement of nanoparticles. The zwitterionic surface of the nanoparticles further helps the transportation across the epithelial layer of the intestine (Zhou Y. et al., 2021). Copyright© 2020, Wiley.

triggered release of Exendin-4 capsules (Figure 8). Exendin-4, the active ingredient in the treatment of diabetes, was efficiently loaded and immobilized on a metal-organic framework (MOF). The amphoteric hydrogel layer coated on the skeleton surface has a unique ability to permeate across the cellular mucus layer and allows for effective internalization of the nanocarrier by epithelial cells. To protect the nanoparticles from destruction in the stomach, a pH-sensitive capsule is used to carry the drug, which is insoluble in an acidic environment and dissolves rapidly in the intestinal fluid, a neutral environment. Based on the fluorescence analysis, MOF nanoparticles led to enhanced absorption of Exendin-4 in the intestine compared to free Exendin-4. After oral administration, the nanoparticles significantly increased the plasma Exendin-4 level and promoted endogenous insulin secretion in diabetic rats, which had significant hypoglycemic effects (Zhou Y. et al., 2021). The use of nanoparticles for insulin transport or gene delivery has also shown excellent therapeutic effects in diabetic model mice (Lamson et al., 2020; Sudhakar et al., 2020). Besides improving

diabetes treatment options, oral nanoparticles have shown great therapeutic promise in other diseases, such as intestinal disorders, bacterial infectious diseases, and oncology (Kim et al., 2019; Shen et al., 2019; Ndayishimiye et al., 2021; Wang J. et al., 2021; Yu et al., 2021; Li et al., 2022; Zhang G. et al., 2022). Additionally, a pioneering attempt to synthesize orally administered nanoparticles has recently been conducted by researchers to easily prepare and use gold nanoparticles (GNP) (Ndayishimiye et al., 2021) in the synthesis conditions. Wang et al. demonstrated that antibacterial GNP (A-GNP) could be synthesized *in vivo* by oral administration of two raw materials: aminophenyl boronic acid (ABA) and tetrachloroauric acid (HAuCl₄). A-GNP has a good antibacterial effect, long half-life (16–17 h), high effective clearance (residual concentration close to 0 *in vivo* within 72 h), and high biosafety (Wang L. et al., 2021).

Notably, the size and shape of nanoparticles show importance in utilizing endocytosis through the gastrointestinal tract and subsequent exocytosis. For example, the large surface area of the

polymer NPs improves the efficiency of drug absorption by increasing the number of interactions with the gastrointestinal tract (Banerjee et al., 2016). The uptake of rod-shaped nanoparticles by epithelial cells is usually superior to that of spherical particles (Banerjee et al., 2016). Pathologies such as inflammation may increase the permeability of the intestinal epithelium and alter mucus production, pH and gastrointestinal microbiota, thus affecting the delivery of nanomedicines (Durán-Lobato et al., 2020).

3.2.2 Inhalation

Pulmonary inhalation is an attractive route of drug delivery in addition to oral and injectable administrations. Therapeutic drugs can be delivered by inhalation into the pulmonary airways to treat diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma, and lung cancer (Edwards et al., 1998; Chow et al., 2007). Physiological and anatomical characteristics of the lungs, such as large absorption area, high permeability of the alveolar epithelial membrane, and high blood flow, make inhalation drug delivery an attractive non-invasive route of administration that avoids drug degradation in the gastrointestinal tract, reduces side effects on normal tissues and organs, and avoids first-pass metabolism in the liver (Kuzmov and Minko, 2015). However, most free drugs, nucleic acids, and peptides used for therapeutic purposes cannot be delivered to the lungs naturally by inhalation. Hence, there has been an increasing interest in delivering drugs to the lungs by inhalation with nanotechnology-based delivery systems.

Although inhaled nanoparticles offer a unique opportunity to treat pulmonary airway diseases, airway physiology and pulmonary clearance mechanisms are key barriers to effective nanoparticle deposition and preservation in the lung (Mangal et al., 2017). The airway surface layer (ASL) is the first line of defense of the respiratory system, protecting the lungs' airways from invasion by harmful foreign substances such as pathogens and pollutants. The ASL consists of the luminal mucus gel layer that covers the airway epithelium and the periciliary layer (PLC). Aspirated foreign bodies, including therapeutic nanoparticles, are readily captured by the mucus gel layer and rapidly cleared from the lungs by mucociliary clearance (MCC), continuous cilia beating of the PLC, or coughing (Chen D. et al., 2021). The mucin glycoprotein in the mucus gel layer has negatively charged O-glycosylated domains. Due to ionic interactions, positively charged nanoparticles cannot pass through the mucus layer (Zhong et al., 2016). The barrier properties of the mucus gel layer are usually more pronounced in disease states. For example, the mucin concentration in the airway mucus of CF and COPD patients is usually elevated, which tightens the mucus mesh spacing and makes it more difficult for nanoparticles to penetrate the airway mucus (Duncan et al., 2016; Chisholm et al., 2019).

Coating nanoparticle surfaces with hydrophilic and neutrally charged PEG polymers to provide an inert mucosal surface can effectively cross the mucus barrier and reduce alveolar macrophage uptake through chemical binding or physical adsorption methods (Huckaby and Lai, 2018). The nanoparticles modified by PEG in the airway mucus of CF and COPD mice exhibited considerable permeability and were able to be uniformly distributed in the airway, and their retention time was significantly prolonged

(Schneider et al., 2017; De Leo et al., 2018; Osman et al., 2018). Recently, PEGylated nanoparticles with efficient transmucosal delivery capacity significantly reduced the development of fibrosis and improved lung function in a mouse model of bleomycin-induced pulmonary fibrosis (Bai et al., 2022). Several PEG alternatives have also been developed to improve the penetration of particles through the airway mucus. Ge et al. used fluorinated polymers containing cationic polypeptides that have a unique ability to resist mucosal adhesion and maintain physiological stability due to fluorination, significantly enhancing the ability of nanoparticles to penetrate mucus. They showed that siRNAs targeting tumor necrosis factor (TNF)- α delivered by fluorinated nanoparticles reduced TNF- α expression and pro-inflammatory responses to a greater extent in the lungs of mice of acute lung injury compared to non-fluorinated formulations that do not penetrate airway mucus (Ge et al., 2020). Self-emulsifying drug delivery systems have been developed as gene-delivery vehicles that can effectively improve the passage through CF airway mucus (Griesser et al., 2019). Recent studies have also shown that ligand modification strategies of nanoparticles using folic acid, transferrin, and neonatal Fc receptor ligand (FcBP) can enhance the lung retention effect of nanoparticles (Rosière et al., 2018; Parvathaneni et al., 2021; Yu et al., 2023). For example, Parvathaneni et al. used transferrin ligand-modified nanoparticles (Tf-AMQ NPs) to treat non-small cell lung cancer, which effectively penetrated the tumor core and inhibited tumor growth. In A549 and H1299 cells, Tf-AMQ NPs significantly induced apoptosis and reduced colony growth % (Parvathaneni et al., 2021).

The physicochemical properties of nanoparticles, such as particle size, can affect their lung retention efficiency (Shen and Minko, 2020). Furthermore, a team has investigated the effect of nanoparticle hardness on pulmonary drug delivery and showed that hard nanoparticles have better endocytosis than soft nanoparticles, which might be related to actin filaments- and Ca^{2+} -mediated endocytosis (Yu et al., 2023). The cytotoxicity of nanomaterials should be considered along with its mucus penetration and lung retention efficiency. Clinical and experimental data suggest that the size and shape of nanoparticles affect their toxicity to the lungs, with smaller nanoparticle sizes and larger surface areas causing more damage to the lungs (Nel et al., 2006; Osman et al., 2020). Besides the physicochemical properties of nanoparticles, alveolar sizes of different sexes, health conditions, and different species might also affect drug inhalation and deposition (Xi et al., 2020). At the same time, for inhalation drug delivery, specific devices for nebulization and inhalation are usually applied. Therefore, how to maintain the specific physicochemical properties of nanoparticles during nebulization without aggregation is an issue to consider during design and preparation (Yhee et al., 2016).

3.2.3 Topical administration

Besides oral and inhalation drug delivery, nano-DDS can also be used for topical administration. In traditional topical drug delivery methods, the residence time and the duration of the drug effect in the tissue are short. Frequent drug administration may increase the risk of local pain and infection (Zhu et al., 2020). Intra-articular administration can significantly increase local drug concentration, prolong the drug's half-life and reduce the adverse effects of systemic drug delivery (Bedingfield et al., 2021; Mao et al., 2021; Wei et al.,

2021). He et al. designed a DDS using pH-sensitive polyacrylic acid (PAA)-modified mesoporous silica nanoparticles (MSNs) loaded with andrographolide (AG) to form the AG@MSNs-PAA nanopatform. The nanoparticles had uniform size (120 nm), high drug loading efficiency [(22.38 ± 0.71)%], and pH-responsive properties (as shown), facilitating their sustained release in osteoarthritis (OA). Moreover, the AG@MSNs-PAA exhibited stronger anti-arthritic efficacy and cartilage protection than AG in cellular assays and OA rat models (He et al., 2021). Intra-articular injection of high-molecular-weight (HMW) HAs is one of the current treatment options for OA. However, the HMW HA treatment can relieve patients' pain but has side effects, such as local inflammation. The mechanism triggering inflammation might be the degradation of HMW HAs into LMW HA molecules by hyaluronidase, associated with increased catabolic gene expression and pro-inflammatory cytokine production (Knudson et al., 2019). Kang et al. (2021) reported a self-assembled hyaluronic acid nanoparticle (HA-NP) as a potential therapeutic agent for OA treatment. HA-NP showed *in vitro* resistance to digestion with hyaluronidase and *in vivo* long-term retention ability in knee joint, compared to free HMW HA. They showed that HA-NP could treat OA by interfering with fragmented LMW HA-CD44 interactions and the underlying mechanisms involved in OA pathogenesis and progression.

One type of non-adhesive nanoparticles (NNPs) consisting of block copolymer poly (lactic acid)-hyperbranched poly (glycerol) (PLA-HPG) can be converted into bioadhesive nanoparticles (BNPs) by brief incubation with sodium periodate (Deng et al., 2016). This treatment alters the chemistry of the HPG molecule, converting vicinal diols into aldehydes, giving them the covalently bonded molecular adhesion that results from the interaction of surface aldehydes with amino groups on biomolecules, such as stratum corneum, the extracellular space, cell surfaces, and the tumor's protein-rich matrix (Thavarajah et al., 2012). BNPs can be used as a local carrier of chemotherapeutic drugs, through intraperitoneal delivery to peritoneal carcinoma, intracranial delivery to brain tumors, and intratumoral delivery to squamous cell carcinoma of the skin, through the skin for psoriasis (Deng et al., 2016; Song et al., 2017; Hu et al., 2021; Mai et al., 2022). They are also used intravaginally to increase the retention of antiviral drugs in the reproductive tract (Mohideen et al., 2017). Nanomaterials have gained attention as drug carriers for transdermal drug delivery. The skin acts as a natural barrier that prevents most drugs from penetrating the highly ordered and dense stratum corneum, limiting the use of transdermal drug delivery. Some lipid nano vehicles and polymeric nanoparticles can overcome the barrier function of the stratum corneum and improve the stability and delivery efficiency of drugs (Lapteva et al., 2014; Sala et al., 2018). Zhao et al. (2022) prepared a highly dispersed DES-MSNs system by modifying citric acid and amino acid on the surface of Mesoporous silica nanoparticles (MSNs), which enables the nanoparticles across SC to the deeper skin layers. This work provides a new strategy for the controlled and sustained delivery of nanoparticles. A recent study found that intraperitoneal injection of anionic nanoparticles can selectively accumulate in TAMs. In a mouse model of metastatic ovarian cancer, fluorescently labeled silica poly (lactic acid-ethanolic acid) and polystyrene nanoparticles selectively accumulated in TAMs. Quantitative absorption of silica particles indicated that

more than 80% of the injected dose accumulated in TAMs. This targeting result was mediated by active, selective uptake by TAMs, and the targeting properties and efficiency are difficult to achieve by intravenous drug delivery (Haber et al., 2020). Other researchers have also infused CAT-TCPP/FCS nanoparticles into the bladder cavity via intravesical perfusion. The results showed that CAT-TCPP/FCS NPs have good transmucosal and intratumoral penetration ability and can catalyze O₂ generation from tumor endogenous H₂O₂ via peroxidase, which can effectively relieve tumor tissue hypoxia and improve bladder efficacy *in situ* tumor under SDT ablation ultrasound (Li G. et al., 2020). Interestingly, it is also possible to spray nanomedicines directly on the surface of the heart. The authors synthesized P/B-COS nanoparticles by loading the glucocorticoid anti-inflammatory drug budesonide (BUD) into PLGA and chitosan (COS) to form a stable saline solution. The anti-inflammatory effect was produced by spraying nanoparticles directly into the local myocardium by catheter saline infusion during atrial fibrillation ablation procedures. Due to the effects of COS, the nanoparticles are positively charged and can better adhere to negatively charged cell membranes, improving the efficiency of local drug delivery (Liu et al., 2022). Topical nanoparticle drug delivery can address the inefficiency of hydrophilic or macromolecular drug delivery and the difficulty to overcome physiological barriers, but these studies are still at the research stage. The translation of such drug delivery is equally limited by the variability between animal models and humans. Although nanoparticle systems have been successfully developed at the laboratory scale, the challenges of scaling up and the lack of reproducibility have made it difficult to achieve conversion from laboratory scale to industrial scale (Gupta et al., 2017).

4 Limitations and challenges of nano-targeted delivery systems

For the specific nature of nanoparticles, nanoparticles researcher has been produced promising results in animal models and *in vitro* studies. However, most research is only at the research stage, the benefits to patients are not nearly enough. The construction of a targeted nanomedicine delivery system is complex task and requires multiple targeting designs that take into account the physiological variables such as blood flow, disease status and tissue structure (Patra et al., 2018). The variability between animal models and humans, the function of nanodrugs in humans is something that is currently difficult for researchers to grasp. Also due to inter-patient heterogeneity, this limitation may make targeted nanoparticles patient-specific in their distribution and function and prevent their widespread use. Notably, the growing popularity of precision or personalized medicine may enable targeted drug delivery systems to play an important role (Collins and Varmus, 2015). The advent of precision medicine minimizes the impact of patient heterogeneity, and the development of individualized treatment plans for each patient can enable nanomedicines to achieve their optimal efficacy. When surface modification of targeted nanoparticles is engineered, the ratio of receptors to ligands needs to be considered so that they can bind adequately to the cell surface. In order to achieve specific targeted drug delivery, the target should be selected in a way that avoids or reduces the

expression of the target on healthy cells. The binding rate between the nanoparticles and the modified molecules should also be considered to avoid side effects caused by unsuitable binding rates (Hoshyar et al., 2016; Kou et al., 2018).

Many studies have attributed the accumulation of nanoparticles in tumors to the EPR effect. However, there are also reports that contradict this conclusion. A recent study utilizing imaging techniques in a mouse tumor model has determined that only a small fraction of nanoparticles accumulation in tumors can be attributed to passive transport, including the EPR effect. Other mechanisms such as immune cell interactions, protein crowns and molecular mechanisms may promote nanoparticles accumulation (Sindhvani et al., 2020). Therefore, while continuing to explore the use of the EPR effect to promote nanoparticle accumulation, the delivery and distribution of nanoparticles should be quantitatively evaluated. Meanwhile tumors and the biological barriers surrounding them may be far more complex to study. Mucus throughout the body, especially in the gastrointestinal tract and lungs, plays a huge role in hindering the delivery of drugs by targeted nanoparticles. In particular, the patient's lifestyle, disease state and other factors can lead to different properties of the mucus, making the barrier faced by the nanoparticles more complex (Wan et al., 2020).

Hybrid nanocarriers are currently one of the most promising tools, as they have different properties in a single system, thus ensuring enhanced performance of the material in the therapeutic system. Nevertheless, the mechanisms of action and toxicity of drug delivery systems are still poorly understood, which provides opportunities for new research. There are still high uncertainties in the clinical application of targeted nanoparticles, such as assessing the safety and toxicity of nanomaterials, the lack of effective regulation, and the stability of nanomedicines when they are introduced into biological systems (Patra et al., 2018).

5 Summary and future outlook

We summarized and discussed the recent application of nanomaterial-based delivery systems in intra- and extravascular diseases. Through different modifications of nanomaterials, such as active targeting, bionanotechnology strategies, and combining exogenous physical triggering strategies, nanomaterials can improve the shortcomings of traditional drugs that are easily cleared in the body with a short half-life and undesirable side effects on vital organs, as well as small molecule drugs that cannot enter the BBB for targeted delivery. Therefore, drug delivery efficiency can improve in vascular diseases, tumors, and neurological diseases by different drug delivery methods. Although the application of nanomaterials has achieved promising therapeutic effects in these diseases, we should pay attention to the heterogeneity of animal models and human diseases and the heterogeneity between different

development periods of the same disease and different patients. We should carefully think before applying animal data to human diseases. To better address this heterogeneity, both treatments and delivery systems can be personalized for specific patients. Future experimental research should consider whether the therapeutic purpose can be achieved and focus on the synthesis and design of nanomaterials. For nanomaterials with relatively simple structures, a clinical translation should also be considered to provide a basis for future nanotechnology development and clinical translation in various clinical diseases. The use of nano-drug delivery systems to deliver precise amount of drug to target cells without interfering with the physiological functions of healthy cells is a trend and goal in the field of research and development for the coming decades. With the development of nanotechnology and delivery strategies, a deeper development of nano DDS is expected for various diseases in clinical practice.

Author contributions

XC wrote the original draft; QX and YS edited the manuscript; QX visualized the figures. YS contributed to the conceptualization, provided funding and supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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