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An EPR-Independent extravasation Strategy: Deformable leukocytes as vehicles for improved solid tumor therapy

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ABSTRACT

Effective delivery of therapeutic modality throughout the tumorous nidus plays a crucial role in successful solid tumor treatment. However, conventional nanomedicines based on enhanced permeability and retention (EPR) effect have yielded limited delivery/therapeutic efficiency, due mainly to the heterogeneity of the solid tumor. Leukocytes, which could intrinsically migrate across the vessel wall and crawl through tissue interstitium in a self-deformable manner, have currently emerged as an alternative drug delivery vehicle. In this review, we start with the intrinsic properties of leukocytes (e.g., extravasation and crawling inside tumor), focusing on unveiling the conceptual rationality of leveraging leukocytes as EPR-independent delivery vehicles. Then we discussed various cargoes-loading/unloading strategies for leukocyte-based vehicles as well as their promising applications. This review aims to serve as an up-to-date compilation, which might provide inspiration for scientists in the field of drug delivery.

Contents

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1. Introduction

Solid tumors, such as breast, lung, colon, prostate, bladder, melanoma, and kidney tumors, account for approximately 90% of human cancers [1,2]. As a dense mass of abnormal and heterotypic cells, solid tumors and corresponding microenvironment (TME) are characterized by biological and pathological natures (e.g. dense extracellular matrix, high interstitial fluid pressure), which might set up stubborn obstacles to efficient treatments [3]. Since the sufficient physical contact between the target cell and therapeutic modality is a prerequisite for an effective solid tumor therapy [4], which means the therapeutic modality must efficiently accumulate, extravasate, and penetrate in tumor tissue to gain enough access to the target cells.

While certain pathophysiological characteristics of solid tumors, such as extensive angiogenesis, defective vascular architecture as well as impaired lymphatic drainage system, have been taken as an opportunity to enhance passive accumulation and extravasation of therapeutic modality into tumor [1,5–8]. Over the past decades, plenty of nanomedicines based on this enhanced permeability and retention (EPR) effect have been developed to improve the accessibility of target cells to drugs [9–11]. In parallel with those passive targeting nanomedicines, active targeting ones could enhance the targeting efficiency through the recognition of functional targeting ligands (such as antibodies, aptamers, or folic acid, etc.) to the corresponding overexpressed receptors on target cells [4,12–14]. Moreover, to further improve the deep penetration of nanomedicine in tumors, strategies such as particle-size shrinking [15,16] or cell-penetrating peptides [17] have also been exerted. Although various nano-strategies aiming at improving the accessibility of target cells to drugs have been developed, the core essence is the classical EPR effect. However, due to the heterogeneity of solid tumor bulk, the abnormalities of tumor blood vessels vary across species and tumor types, and even stages of tumors. More and more researchers are raising doubts on the contribution of EPR effect to the accumulation as well as extravasation of nanomedicine in tumor recently [18,19]. Of note, Warren Chan and colleagues found that an average of 0.7% of systemically administrated nanomedicines reached solid tumors. Efficient drug delivery paradigms for solid tumor therapy are thus still challenging [20].

Leukocytes, also called white blood cells, are cells involved in protecting the body against infectious diseases and other foreign invaders [21,22]. As immune defenders, the leukocytes exhibit excellent tropism to the inflammatory or damaged sites in a self-deformable manner [21]. Notably, tumor has been widely recognized as an unresolved chronic inflammation disease [23,24], establishing a chemokine gradient to recruit various leukocytes such as neutrophils (NEs), macrophages, mast cells, myeloid-derived suppressor cells, dendritic cells, natural killer cells, T and B lymphocytes [25,26]. The natural inflammation-tropism as well as the relatively large intra- and extra-cellular space, makes leukocytes hot candidates for anti-tumor vehicles [27,28]. To get a comprehensive understanding of this paradigm-shifting drug delivery strategy, i.e., leukocyte-based vehicles, we start with the intrinsic properties of leukocytes (e.g., extravasation and crawling inside tumor), focusing on unveiling the conceptual rationality of leveraging leukocytes as EPR-independent delivery vehicles. Then we discussed various fabrication strategies for leukocyte-based vehicles as well as their promising applications. The limitations and prospects of leukocyte-based vehicles in tumor therapy are also discussed. This review aims to serve as an up-to-date compilation, which might provide inspiration for scientists in the field of drug delivery.

2. Leukocytes in inflammation and tumor

As a hallmark of inflammation, the migration of leukocytes from circulation to inflamed tissue is intriguing. The classical leukocyte migration and infiltration processes include endothelium adhesion and transendothelial migration. In this section, we focus on the intrinsic properties of leukocytes including inflamed-tissue tropism, vessel extravasation, and crawling inside interstitium, and unveil the conceptual rationality of leveraging leukocytes as EPR-independent delivery vehicles[29].

2.1. General steps for the extravasation cascade of leukocytes

It is now firmly established that the extravasation cascade of leukocyte is initiated upon endothelium adhesion, and then transendothelial migration occurred, which is accompanied by dramatic shape changes of leukocytes for crawling across interstitium in inflamed tissue.

Endothelium adhesion. The inflammatory cytokines or chemokines (such as tumor necrosis factor-α (TNF-α) or interleukin-1β (IL-1β)) in inflamed tissue stimulate the overexpression of leukocyte integrins, such as leukocyte function-associated antigen 1 (LFA1, also known as αLβ2 integrin) or VLA4 (also known as α4β1 integrin) [30]. While, under the same stimulation, the expression of corresponding integrin ligands on vessel endothelial cells are also highly increased, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM1) [29,31]. Consequently, adhesion and tethering of leukocytes onto endothelium are established based on integrin-ligand binding [31,32], which is further strengthened and results in rolling and sticking of leukocytes on the vessel endothelium [33,34].

Transendothelial migration. After the leukocytes are fully adherent to the blood vessel, and reach an appropriate site for transmigration (preferably the intercellular junctions), they polarize and extend finger-like protrusions between two adjacent endothelial cells [35]. Then they transform across the open space on the monolayer [36]. Except for this paracellular route, accumulating evidences show that leukocyte can migrate through individual endothelial cells (transcellular route) without perturbing the interendothelial junctions, which occurs preferentially in the microvasculature, the blood–brain barrier, or high endothelial venules of the secondary lymphoid organs [37–40].

In summary, in response to the concentration gradient of cytokines or chemokines, circulating leukocytes are recruited to the inflamed site through the interaction of adhesion molecules between leukocytes and endothelial cells. Subsequently, leukocytes migrate across the vessel wall [41], and make their way to deep tissue in a deformable manner.

2.2. Leukocytes in tumor

Tumorigenesis processes are always accompanied with inflammation, hypoxia, and necrosis, which cause related cytokines secretion and thus induce the recruitment of leukocytes into the tumor site [42]. Notably, the inflammatory cells (such as neutrophils, macrophages, mast cells, myeloid-derived suppressor cells, dendritic cells, natural killer cells, T and B lymphocytes, etc.) are important cellular components of tumor microenvironment (TME) [25,36,43]. For example, according to The Cancer Genome Atlas (TCGA) data, neutrophils accounts for 4.5% of total cells in breast tumor. The neutrophil ration is 5.8% and 5.0% in colon and pancreatic tumor, respectively.

Key players in extravasation cascades of leukocytes, including TNF-α or IL-1β are generally presented in solid tumors [44]. Additionally, the endothelial cell of tumor blood vessel highly expresses

the adhesion molecules, ICAM-1 and VCAM1 [45,46]. Therefore, the migration of leukocytes from circulation to tumor probably follows the same cascades as other inflammation diseases [47,48]. Following transendothelial migration through vascular endothelium, the leukocytes form a protrusive edge for migrating across the tissue fibrillar network extracellular environment (ECM) [49,50]. These polarization and motion processes involve a redistribution of cytoskeletal protein (such as F-actin) of the cell, driving persistent directional motility to pass through the ECM over the interstitium [36,51]. Such 'amoeboid' movement, in which cells undergo rapid shape change during locomotion for passing through interstitium, may greatly contribute to the distribution of leukocytes in both vessel- rich or poor regions of tumors. Taken together, as the key contributors to tumorigenesis [26], the leukocytes could exploit the inflammatory microenvironment in tumor (tumor tropism) to extravasate blood barrier (extravasation), crawl inside the ECM (tumor infiltration), and overcome the high interstitial fluid pressure (Fig. 1).

3. Leukocytes used as anti-tumor drug delivery vehicles

Considering the active recruitment of leukocytes by inflamed tumor, these leukocytes could be leveraged as delivery vehicles [25,36,43]. Theoretically speaking, the mechanism of leukocytes transporting therapeutics across blood vessel barrier is therapeutically based on the extravasation of leukocytes, bypassing the EPR effect, which includes several steps as follows [33]. Firstly, leukocytes with loaded therapeutics are activated by the inflammatory factors released from tumor sites. Secondly, leukocytes together with therapeutics swarm to the cytokines and chemokines gradient, and further increase exposure of adhesion molecules on both endothelial cells and leukocytes. After that, leukocytes together with therapeutics can be captured by the endothelial cells due to the increased expression of adhesion molecules, and thus promoting endothelium adhesion. Finally, based on the transformable ability of leukocytes, they can transform across the open space on the monolayer together with loaded therapeutics. Leveraging these merits, leukocytes served as drug vehicles may effectively deliver therapeutics into tumors, utilizing the extravasation as the most promising strategies alternative to the EPR effect [33,35].

Since the loaded therapeutic agents are supposed to have no effect on physiological functions of leukocytes, such as the chemotaxis, transvascular capacity, and so on [31,52–55]. To fully understand the transporting mechanisms of leukocyte-based vehicles, whether following exactly the same pathways of leukocytes or new tricks, the development of *in vivo* imaging technologies such as positron emission tomography or intravital microscopy has been applied. Based on these novel technologies, we could visualize how the leukocytes transport drugs across the tumor blood vessels [56,57]. Taking neutrophils as an example, iron oxide nanoparticles hijacked neutrophils, and crossed the tumor vascular barrier together with neutrophils [56]. Moreover, in another study, extravasating neutrophils opened the tumor vascular barrier, leading to the enhanced leakage of liposome into the tumor tissues [53,58]. Notably, to the best of our knowledge, there have few studies on *in vivo* evidences about how the leukocytes broke the ECM or IFP barriers to deliver drugs into deep tumor tissues. So was the transporting mechanism for other types of tumor-infiltrating leukocytes, such as T cells, monocytes/macrophages etc.

Here, we discussed the main types and properties of leukocytes currently being developed as leukocyte-based vehicles, including

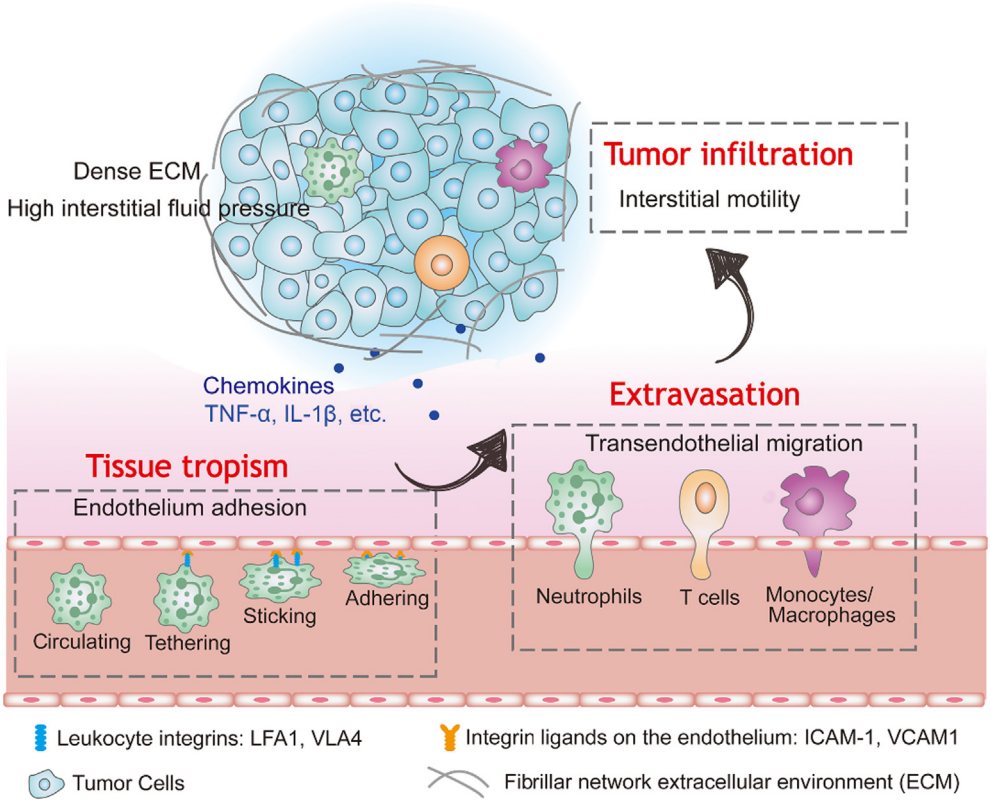

Fig. 1. The recruit cascade of leukocyte in inflamed tumor.

neutrophils, monocytes/macrophages, T cells, and natural killer cells (NK cells) (Table 1) [59,60].

3.1. Neutrophils

Neutrophils, as the most abundant leukocytes (50–70% of the total leukocytes in circulation), serve as the first line of immune defense in circulation [81]. During infection or acute inflammation, neutrophils rapidly respond to the gradient of inflammatory factors and swarm to the inflammatory site, after which they kill pathogens through direct phagocytosis, degranulation, or the formation of neutrophil extracellular traps (NETs) [82]. Notably, accumulated researches have demonstrated that neutrophils exhibit inherent tumor-homing ability and remarkable infiltration in tumor tissue, as evidenced by the cluster of neutrophils (so called tumor-associated neutrophils (TANs)) in tumor tissues [83–85]. TANs exhibit both tumor-promoting and -inhibiting phenotypes. Pro-tumor neutrophils support tumor angiogenesis and growth. Besides they promote metastatic dissemination of tumors via establishment of the premetastatic niche. In contrast, the anti-tumor TANs secret H_2O_2 to kill tumor cell [86]. Other anti-tumor mechanisms, such as Fas ligand/Fas interaction, are also demonstrated [87].

As the significant phagocytes for clearing pathogens, bacteria, or other exogenous particles, neutrophils can naturally encapsulate the therapeutic modalities, giving a ride for these therapeutics. However loaded cargos should go through the harsh microenvironment inside neutrophils, including the abundant enzymes-which are supposed to slaughter the invading pathogens or bacteria. The fragility of neutrophils, especially the short life-span, i.e. 6–8 h, requires a exquisite and benign loading technique [88]. At the same time, this short-life span can spare the concerns related to the phenotype plasticity in tumor, when taking neutrophils as the delivery vehicles.

3.2. Monocytes/Macrophages

Monocytes are derived from bone marrow progenitor cells. Circulating monocytes can migrate and infiltrate into tissues following the gradient of inflammatory factors such as microbial products, inflammatory chemokines/cytokines. Monocytes recruited into inflamed tissues differentiate into macrophages [89], which play versatile roles in inflammation defense, cytokine secretion, and microbe/cellular debris clearance. It has been demonstrated that the hypoxia and necrotic areas in the center of tumors have elevated expression of inflammatory chemokines, which recruit monocytes/macrophages [90]. Tumor-associated macrophages (TAMs) represent one of the main tumor-infiltrating immune cell types, and are generally categorized into classical activated M1 macrophages and alternatively activated M2 macrophages [59]. The former one typically exerts anti-tumor functions, including phagocytosis and antibody-dependent cell-mediated cytotoxicity (ADCC); the latter one can promote the occurrence and metastasis of tumor cells, inhibit T cell-mediated anti-tumor immune response, promote tumor angiogenesis, and lead to tumor progression [26,92–95].

Similar to neutrophils, the superior phagocytosis capability of macrophages on one hand makes the therapeutic loading facile, and on the other hand sets a higher requirement on the stability of delivered therapeutics. Moreover, the fate of carrier macrophages after finishing the delivery task, e.g. phenotype change, needs more attention.

3.3. Lymphocytes

Lymphocytes are the second-largest subtype of leukocytes in human, accounting for 30% of white blood cells of human, which includes T lymphocytes (T cells), B lymphocytes (B cells), and natural killer cells (NK cells) [91]. In response to pathogen infection, NK cells, as innate immune cells, produce lytic granules containing molecules (perforin, granzymes, etc.) that can induce cell death in pathogen-infected cells. They also express several tumor necrosis factor (TNF) superfamily members, such as FASL and TRAIL, which induce apoptosis of target cells via binding to their corresponding receptors FAS or TRAILR, respectively [92].

For tumor immunotherapy, lymphocytes are engineered to express chimeric antigen receptor (CAR), e.g., CAR-T and CAR-NK. These CAR-lymphocytes display an augmented tumor recognition ability, which might be advantageous for targeted cargo delivery [93,94]. Additionally, from a point of view of clinic translation, the clinically approved CAR-T products would be the superior choice of drug vehicles.

4. Therapeutic-Loading methods

The therapeutic modality can be loaded into/onto leukocytes *ex vivo* or *in vivo* (Fig. 2A). *Ex vivo* loading, also referred to cytopharmaceutical [95], involves the manipulation of leukocytes for drug loading *ex vivo*. And *in vivo* loading strategy uses tailor-made nanomedicines to target the circulating leukocytes and get a ride to the tumor sites *in vivo* [96], for which design of targeting cargos matters. Whichever kind of loading method is, the interactions between delivered cargos and carrier leukocytes should be clarified in detail, thus yielding a facile, efficient, and robust loading method for leukocyte-based vehicles. The comparison of different therapeutic loading strategies has been summarized in Table 2.

Table 1
Types of leukocytes used as anti-tumor drug delivery vehicle.

	Neutrophils	Macrophages/monocytes	Natural Killer Cells	T cells
Location	Peripheral blood, inflammatory tissue, carcinomatous parenchyma, metastasis node [61,62]	Bone marrow, peripheral blood, inflammatory tissue, carcinomatous parenchyma, metastasis node [63,64]	Bone marrow, peripheral blood, liver, spleen, lung, lymph nodes [65,66]	Lymphoid tissues (bone marrow, spleen, tonsils, and lymph nodes), mucosal sites (lungs, small and large intestines), and skin [67]
Amount	0.8–1.5 × 10^9/L in adults	2–8 × 10^8 /L in adults	greater than1 × 10^8 /L in adults	0.64–1.18 × 10^9/L in adults
Lifespan	6–8 h ($t_{1/2}$)	Ly6c^{high}: 17 h ($t_{1/2}$) Ly6c^{low}: 2–14 days ($t_{1/2}$)	1 week	2 weeks after activation
Pros as vehicles	Widely sourced, phagocytosis for drug loading, rapid recruitment [68,69]	Phagocytosis for drug loading, anti-tumor properties [70]	Engineered NK cells expressed with chimeric antigen receptor (CAR), solid tumor infiltration, direct tumor killing [71–73]	Engineered T cells expressed with chimeric antigen receptor (CAR) or chimeric antigen receptor (TCR), direct tumor killing [74,75]
Cons as vehicles	Short lifespan [76]	Various phenotypes [77]	Non-phagocytic	Non-phagocytic, poor tumor infiltration [78–80]

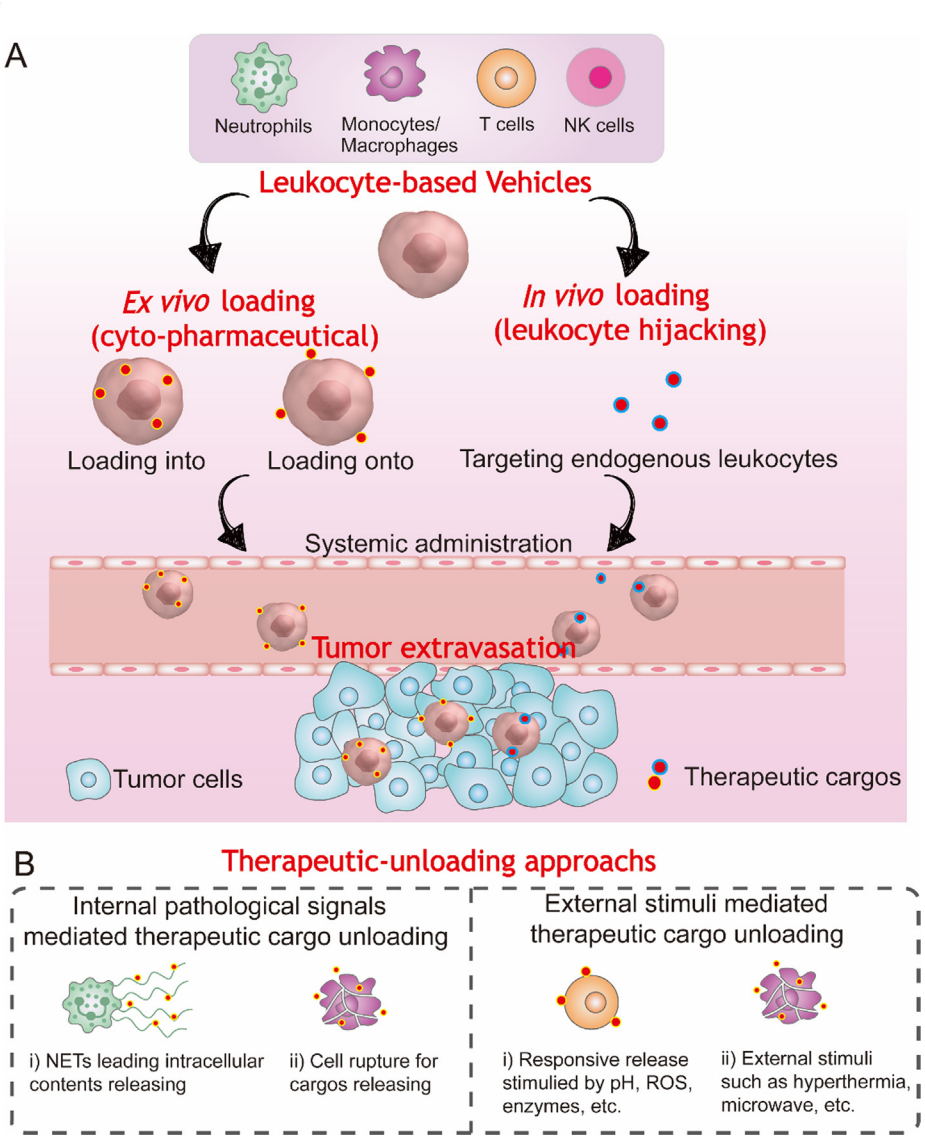

Fig. 2. Therapeutic- loading (A) and unloading (B) approaches.

Table 2
Comparison of different therapeutic-loading strategies.

Loading strategies	Drug-loading methods	Drug-loading occasion	Carrier Leukocytes	Remarks
Ex vivo loading (Cytopharmaceutical)	Encapsulating the cargos within leukocytes *ex vivo* "Loading into"	Utilization of the phagocytic activity to internalize the cargos into cellular compartments	Phagocytic cells (neutrophils, monocytes/ macrophages)	Accurate control of drug loading ratio; Easy-to-prepare; Limited to phagocytes.
	Backpacking the cargos onto the surface of leukocytes *ex vivo* "Loading onto"	Noncovalent attachment (electronic adsorption, hydrophobic anchoring, ligands/receptors interaction); Covalent conjugation (click chemistry)	Nonphagocytic cells (T cells, NK cells)	Relatively low requirements on stability of cargoes, General, especially suitable for nonphagocytes
In vivo loading (Cell hitchhiking)	Targeting the endogenous circulating leukocytes *in vivo*	Endocytosis or adsorption	Neutrophils; Monocytes/ macrophages	Strict requirements on targeting ability of cargoes; Easy -to-prepare; Cost- and labor-saving.

4.1. Ex vivo loading (cyto-pharmaceutical)

Cyto-pharmaceutical is to harvest leukocytes from autologous patients or allogeneic donors, which are subsequently loaded with therapeutic modality *in vitro,* and transfused back into patients [97]. Manipulation of harvested leukocytes plays vital roles in this loading method. Depending on the cellular location of the therapeutics, there are two ways of cargo-loading: i) internalization of the cargos within leukocytes (“loading into” strategy), ii) backpacking the therapeutic modality onto the surface of leukocytes (“loading onto” strategy) [95].

“Loading into”. The most facile method for loading therapeutic modality is to utilize the phagocytic activity of leukocytes. This method is likely limited to certain kinds of phagocytic cells, such as neutrophils or macrophages. Our group has leveraged the natural phagocytic capacities of neutrophils to fabricate neutrophil cyto-pharmaceuticals of liposomal paclitaxel (PTX) or albumin-bound PTX nanoparticles (Abraxane) without a loss of cellular viability during circulation [98]. The loading efficiency of this method is probably comprised given the necessities to maintain the intact physiological functions of leukocyte vehicles. To further improve the internalization of therapeutics into leukocytes, utilization of the ligand-receptor effect is under development. For example, hyaluronic acid-functionalized iron oxides were massively loaded into macrophages via the interaction of hyaluronic acid and CD44 receptors on macrophages [99]. Alternatively, improving the drug content per nanoparticle was also developed. Porous silica nanoparticles with super-high doxorubicin (DOX) content were phagocytosed by macrophages to yield a macrophage cyto-pharmaceutical with enhanced loading efficiency [100].

Except for the loading efficiency, the interaction between the internalized therapeutic modality and leukocyte should be also considered. From the perspective of loaded cargos, they must survive in the harsh intracellular microenvironment, including abundant enzymes and the acidic pH of endosomes/lysosomes; While from the perspective of vehicle leukocyte, the loaded cargos should stay inert and do little harm to the vehicle cell. Taking together, the nanotherapeutic might be the suitable form to use this “loading into” method, as the nanocarrier provides a protecting shell for both leukocyte and therapeutic.

“Loading onto”. Limited by the poor endocytosis ability of lymphocytes, encapsulating therapeutics within cells is not applicable for lymphocytes-based vehicles. The “loading onto” technology are thus attractive for lymphocytes-based ones, which are divided into two classes: non-covalent anchoring and covalent conjugation. The former one involves the use of electronic attraction as well as the ligand-receptor recognition between the cargo and the vehicle leukocyte [101,102]. However, the physical interaction, namely the electronic or ligand-receptor effect, might not be strong enough to maintain the backpacked cargos on cell surface under the physiological flow conditions. Complementarily, the covalent conjugation method involves the conjugation chemistry between the pair reactive groups in cell surface (either naturally available or exogenously introduced) and cargos. For example, free thiol or amino on cell surface proteins provides conjugation sites for maleimide or N-Hydroxysuccinimide functionalized cargos. A T cell cytopharmaceutical of 7-ethyl-10-hydroxycamptothecin (SN38) was fabricated via the covalent conjugation of maleimide-functionalized nano SN38 to the cell-surface thiols [103]. However, the modification of nature proteins might damage the physiological functions of T cells. Further, based on click chemistry and membrane insertion of functional lipid, our group conjugated the bicyclo [6.1.0] nonyne (BCN) functionalized liposomal avasimibe onto tetrazine (Tre)-modified T cell surface by the BCN-Tre click chemistry [104].

For “loading onto” methods, the therapeutic modality must not be internalized by the vehicle leukocyte. Several techniques have been developed: i) using the non– or slow- internalizing receptor as the cargo anchor. For example, IL-15 nanogel containing a small quantity of anti-CD45 was non-covalently attached onto T cell, using non-internalizing CD45 receptor on T cell as the anchor [105]; ii) using phagocytosis-resistant nano cargos. For instance, 77.3% of the initially anchored interferon γ (IFN-γ) backpacks (with an anisotropic shape) remained on macrophage over 5 days [106].

It’s worth noting that we should not fall into a pure pursuit of high loading efficiency. Since when too many cargos are loaded onto the leukocyte surface, the behaviors of leukocytes, such as recognition of antigen, chemokines, or cytokines, might be impaired. Additionally, the crosstalk with other cells would be impacted too. For instance, accelerated clearance by endogenous macrophages might occur. However, studies on the critical loading point of each leukocyte vehicle have been scarce, which deserves a detailed investigation in the future.

4.2. In vivo loading (leukocyte hijacking)

Compared with the tedious preparation processes of cyto-pharmaceuticals, including leukocyte collection, cargo loading, quality control etc, the relatively facile *in vivo* loading strategy, i.e. endogenous leukocytes “hitchhiking”, has attracted lots of attention. “Hitchhiking” strategies means using the finely-designed nanomedicines to target the endogenous circulating leukocytes *in vivo* and get a ride to the tumor sites [96]. Most of the targeting strategy is based on ligand-receptor recognition. For example, the intravenously administrated anti-CD11b antibodies modified gold nanorods targeted to the circulating neutrophils and thus achieving a higher accumulation into tumor tissue [97]. Besides, sialic acid, as the small molecular ligand for selectins on leukocytes, was also deployed to hijack circulating leukocytes *in vivo* [107]. Except for the ligand-receptor targeting strategy, the natural phagocytic capacity to take up invading bacterial or endogenous wastes of monocytes/macrophages can also be exploited for drug-loading *in vivo*. Apoptotic bodies of tumor cells with a diameter of 1–5 μm as well as bacterial-membrane coating cargos have been developed to target circulating monocytes/neutrophils, realizing drug loading *in situ* [108].

In summary, with a “bacteria-mimic” surface or specific ligands, cargoes can be easily internalized *in situ* by the circulating leukocytes, e.g., neutrophils, monocytes. Although this strategy is relatively cost- and labor- saving, many critical issues remain unsolved. For example, the intravenously administrated cargoes not only interact with the targeted leukocytes, but also with other components in circulation, e.g., proteins, which might lead to the insufficient hijacking efficiency. Along with this issue, how to decide the dosage? In addition, does the interaction of cargoes with leukocytes lead to the cellular internalization or cell-surface attachment?

4.3. Therapeutic-unloading approaches

For a complete drug delivery loop, the cargoes should be unloaded at tumor site to get access to their target cells. For the “loading into”-based leukocyte vehicle, the cargos need to overcome two barriers (including cellular and nanoparticulated barrier) to get free; while similar to traditional nanomedicine, cargoes released from “loading onto”-based leukocyte vehicles require overcoming the nanoparticulated barrier. No matter which release profile is, a timely and complete cargo release model is preferred. To the best of our knowledge, there have been two ways of therapeutic unloading: external stimuli or internal pathological signals mediated ways (Fig. 2B).

When referring to the release of cargoes from **"loading into"-based leukocyte vehicles**, the sequence of overcoming each barrier matters. In response to inflammatory cytokines, neutrophils can form neutrophil extracellular traps (NETs) *via* expulsion of intracellular contents (including the neutrophil's DNA and associated proteolytic enzymes), which can facilitate the cargoes escape from the cellular barrier. For example, in the post-surgical residual glioma, the neutrophil-based vehicles containing liposomal PTX split out the liposomal PTX via the formation of NET [98]. For other leukocytes, whose natural cellular responses to inflammation are not involving the rupture of cell, they can exploit the cargoes (escaping from the nanoparticulated barrier first) to damage the vehicle cell integrity. For example, leveraging the overexpressed protease legumain during the differentiation of monocytes into macrophages in metastatic tumor, the cargoes first released from the legumain-sensitive nanocarrier, and subsequently damaged the vehicle monocyte to complete the release profile [109]. Qi et al. locally applied microwave to trigger the release of DOX from thermal-sensitive micelle (loaded into monocyte) first, which subsequently damaged the monocyte vehicle, and in turn, facilitated its own escape from cellular space [110].

"Loading onto"-based leukocyte vehicles. The diffusion of cargoes from backpacked nanocarrier into target cell is the most convenient way, without a complex design of nanocarrier. Our group backpacked liposomal Avasimibe onto T cell, which displayed a sustained Avasimibe release over 3 days [104]. However, for other cargoes, whose activity depends on a high concentration in a short time, a stimuli-responsive and burst release profile is preferred. For example, the nanogels containing interleukin-15 that responded to an increase in T cell surface reduction potential after activation, were anchored onto the T cell surface [105]. The release of interleukin-15 was tumor-specific and improved the therapeutic window. Similarly, by exploiting the acidic pH after the formation of an immunological synapse (IS), the pH-sensitive micellar DOX conjugated onto NK cell surface solely released DOX when NK cells attacked cancer cells [111].

5. Current applications of leukocyte-based vehicles

Inheriting the chemotaxis of leukocytes towards inflammation, leukocyte-based vehicles hold the enhanced ability of tumor targeting and deep penetration through an EPR-independent way. The inflammation signals for leukocytes chemotaxis could be produced solely by tumor tissues or other inflammation-proving therapeutical modalities. The representative leukocyte-based vehicles, their applications, and remarkable advantages are summarized in Table 3.

5.1. Recruited by tumor-related inflammation signals

As discussed in Section 2, primary or metastatic tumor *per se* can produce and release a series of inflammatory chemokines and cytokines, which can effectively recruit the leukocytes-based vehicles. Based on this EPR-independent extravasation strategy, leukocyte-based vehicles can largely improve the efficacy of current anti-tumor modalities, such as chemotherapy, photothermal/photodynamic therapy (PTT/PDT), immune therapy, and even combinational therapy.

Chemotherapy. Small molecular cytotoxic agents, e.g., PTX, DOX, and cisplatin, have been used to kill tumor cells in a dosage-dependent manner. However, the limited accumulation and uneven distribution of these cytotoxic agents in tumor tissue severely restrict their effectiveness in solid tumor therapy. Taking the advantages of leukocytes-based vehicles including effective

Table 3
Representative leukocyte-based vehicles and their applications.

Carrier Leukocytes	Loading Strategies	Disease Model	Therapeutics	Remarks	Ref.
Neutrophils	*Ex vivo* loading (Cyto-pharmaceutical)	Post-surgical glioma	Liposomal paclitaxel	Inflammation/injury targeting for complementary therapy of post-surgical glioma, crossing blood–brain barrier (BBB)	[98]
		Breast cancer lung metastasis	Transforming growth factor-β (TGF-β) receptor inhibitor	Lung metastasis targeting, primary and metastatic cascades suppression	[112]
	In vivo loading (leukocyte hijacking)	Breast cancer	Podophyllotoxin-loaded mycoplasma membrane-fused liposomes	Breast cancer targeting	[96]
Monocytes/ macrophages		Post-photodynamic therapy	Anti-CD11b-decorated nanomedicine	Drug delivery for photodynamic therapy	[97]
	Ex vivo loading (Cyto-pharmaceutical)	Lung metastasis	Liposomal doxorubicin	Lung metastasis targeting	[113]
		Primary and bone metastatic tumors	Oxaliplatin prodrug and Zinc phthalocyanine photosensitizer	Lung metastasis targeting, primary and metastatic cascades suppression	[114]
	In vivo loading (leukocyte hijacking)	Breast cancer	Micelles co-loaded with doxorubicin and the A2AR antagonist	Drug delivery to breast cancer for enhanced immunotherapy	[110]
		Lymphoma and metastasis	CpG immunoadjuvant-modified gold-silver nanorods	Drug delivery to lymphoma and metastasis for enhanced immunotherapy	[108]
T cells	*Ex vivo* loading (Cyto-pharmaceutical)	Melanoma with lung and bone marrow metastasis	Interleukin-15 (IL-15) and IL-21	Maintaining the function, phenotype, and/or lifespan of T cells for increasing the immune response	[103]
		Melanoma	Human interleukin (IL)-15 super-agonist (IL-15Sa)	Maintaining the function, phenotype, and/or lifespan of T cells for increasing the immune response	[105]
		Melanoma	Liposomal Avasimibe	Inducing rapid T cell receptor clustering and sustained T cell activation	[104]
NK cells	*Ex vivo* loading (Cyto-pharmaceutical)	Metastases in the tumor-draining lymph nodes	Liposomes loaded with apoptosis-inducing ligand TRAIL	Targeting metastases in the tumor-draining lymph nodes for enhanced chemotherapy	[115]

extravasation and penetration, Choi et al. has reported a macrophage cyto-pharmaceutical of liposomal DOX [113]. After a systemic administration, this macrophage-based system successfully gathered to subcutaneous xenograft tumor models and penetrated deep into the hypoxic region. Efficient delivery of chemotherapeutic drugs into tumor tissue led to significant inhibition of tumor growth. Additionally, efficient drug delivery to metastatic tumor is also a bottleneck in tumor treatment due to the micro size and discrete distribution of metastatic loci. For example, macrophage-based cytopharmaceuticals of DOX have been developed for treatment of metastatic ovarian carcinoma (Fig. 3) [116]. With the upregulated expression of CCR2 and CCR4 on the M1 macrophage surface, these macrophage-based vehicles significantly enhanced the infiltration of DOX into the disseminated peritoneal tumor nodules, compared to liposomes. Moreover, M1 macrophage-based vehicles exhibited substantial penetration throughout the tumor parenchyma at a distance of more than 1000 μm, which was significantly deeper than that of liposomes (approximately 200 μm). The improved accumulation and distribution of DOX within metastatic ovarian carcinoma of macrophage-based vehicles prolonged the overall survival time of the metastasis-bearing mice.

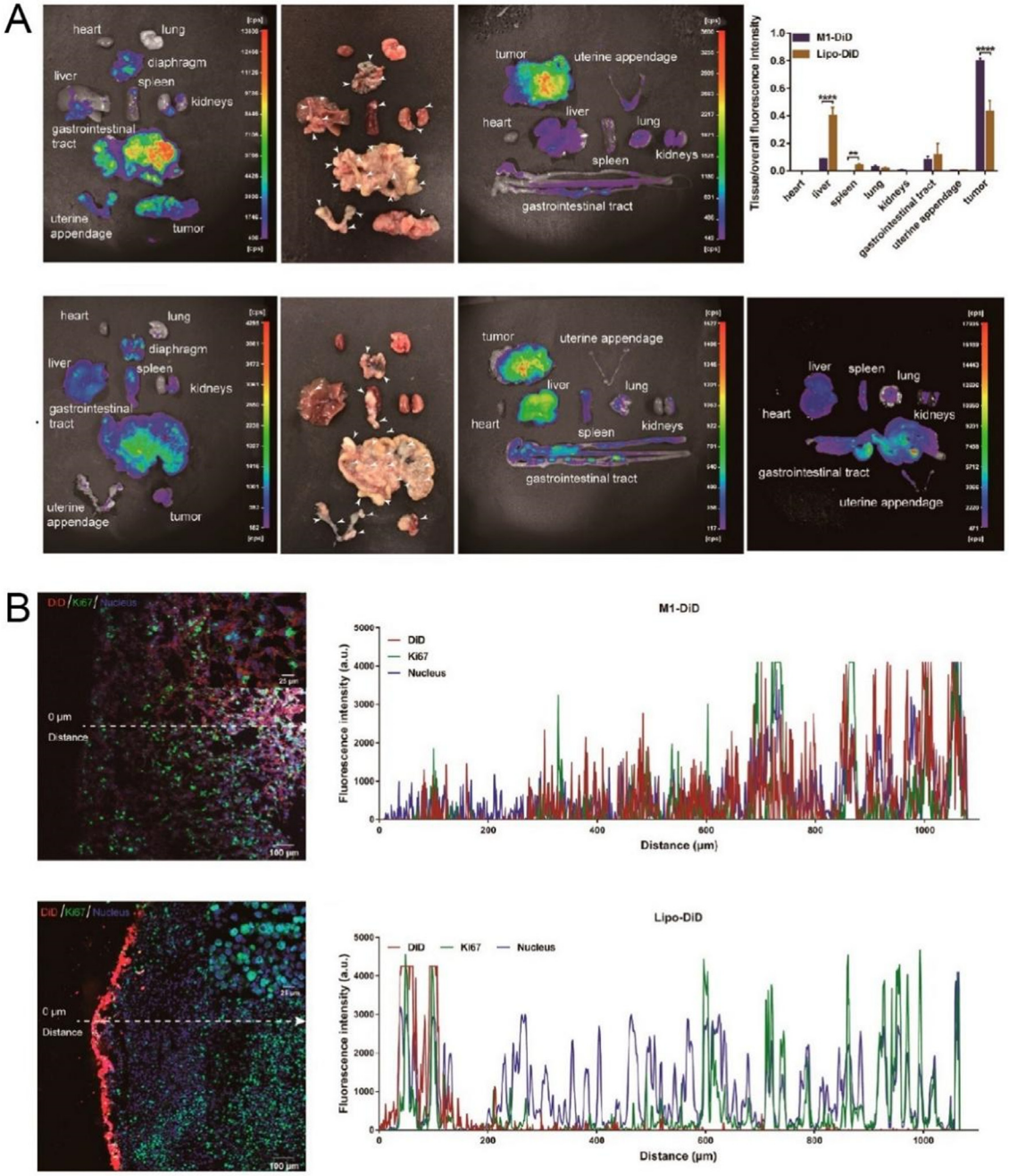

Fig. 3. Monocyte/macrophage-based vehicles targeting to metastatic nodules in the advanced ovarian carcinoma mouse model. (A) Representative fluorescence images and biodistribution of excised organs at 24 h post-injection of macrophage-based vehicles (M1-DiD) or DiD-labeled Liposomes (Lipo-DiD). (B) Representative sections of the metastatic tumor tissue from tumor-bearing mice at 24 h after i.p. administration of macrophage-based vehicles (M1-DiD) or Lipo-DiD (red fluorescence), and the quantification of fluorescence intensity across the metastatic tumor tissue. Reprinted with permission from [116]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

It is worth noting that, most of the cargoes used in chemotherapy can attack target cell and the vehicle cell without discrimination. Exquisite design of the cargoes is needed to avoid the undesired damage to vehicle cell, and meanwhile have enough access to target cell.

PTT/PDT. Except for chemotherapy, leukocyte-based delivery of photosensitizer for solid tumor therapy was also developed. For instance, anti-CD11b-coated gold nanorods were administered to a tumor-bearing mouse, subsequently captured by the circulating neutrophils, and accumulated into tumor tissue via the ride of neutrophils [117]. The enhanced delivery of gold nanorods into tumor dramatically decreased tumor growth and increased survival time of tumor-bearing mice. Additionally, in a hard-to-reach GL261 glioma mice model, a monocyte cyto-pharmaceutical of photosensitizer (Pt (II) octaethylporphyrin) was intravenously administrated, crossed the BBB, and killed the GL261 glioma cell via PDT [118].

Immunotherapy. Immunotherapy has become a powerful clinical strategy for tumor treatment. Immune-stimulating agents, e.g. transforming growth factor-β (TGF-β) inhibitors, interleukin (IL)-12, have attracted lots of attention, due probably to the super immune-eliciting activity. Considering the severe immune-related toxicities, a concise and efficient delivery system for immunotherapy is needed. For instance, a neutrophil cyto-pharmaceutical of liposomal SB525334 (TGF-β receptor inhibitor) simultaneously migrated into both primary and metastatic tumor sites after a systemic injection, released SB525334 in response to inflammatory stimuli, and contextually inhibited epithelial-mesenchymal transition and phenotype reversal of both the carrier and endogenous neutrophils [112]. Mediated by the simultaneous delivery of immune-stimulating agents into primary and metastatic tumor sites, this neutrophil cytopharmaceutical blocked several steps in the metastatic cascade, and thus exhibited a substantial anti-metastasis efficacy. Additionally, Hao et al. reported a T cell cytopharmaceutical of liposomal Avasimibe for maintaining the anti-tumor potency of transfused T cells in the immunosuppressive microenvironment of melanoma and glioblastoma (Fig. 4) [104].

Except for small molecular agents, Stephan et al chemically conjugated multilamellar lipid nanoparticles containing IL-15 and IL-21 onto T cell surface [103]. These adjuvant nanomedicines loaded onto cell surface could directly amplify the therapeutic functions of adoptive transferred T cells, and result in complete elimination of the disseminated B16F10 melanoma with lung and bone marrow metastasis (Fig. 5A). A similar attempt has also been made by Tang et al., [105] using adoptive T cells to deliver IL-15Sa (Fig. 5B). This T-cell based vehicles led to enhanced T-cell persistence and function, which highly improved the therapeutic window of CAR-T cell therapy *in vivo*.

Additionally, Zheng et.al has developed the apoptotic bodies encapsulating CpG-modified gold-silver nanorod. After a systemic injection, they were selectively phagocytosed by circulating Ly-6C$^+$ monocytes and then infiltrated into the tumor center [108]. This "hijacking" strategy of apoptotic bodies contributed to an enhanced and deep intratumor distribution of immune-stimulating CpG, and thereby leading to an effective anti-tumor immune responses.

Combinational Therapy. Leukocytes-based vehicles have been leveraged to deliver synergistic therapeutics to efficiently eradicate solid tumor. As reported by Huang et al., nanomedicines containing oxaliplatin prodrug and Zinc phthalocyanine photosensitizer (Oxa(IV)@ZnPc) were encapsulated into bone marrow-derived macrophages for tumor chemo-photodynamic therapy [114]. These macrophage-based cyto-pharmaceuticals exhibited high drug loading efficiency with intact cellular functions. After an intravenous injection, the macrophage

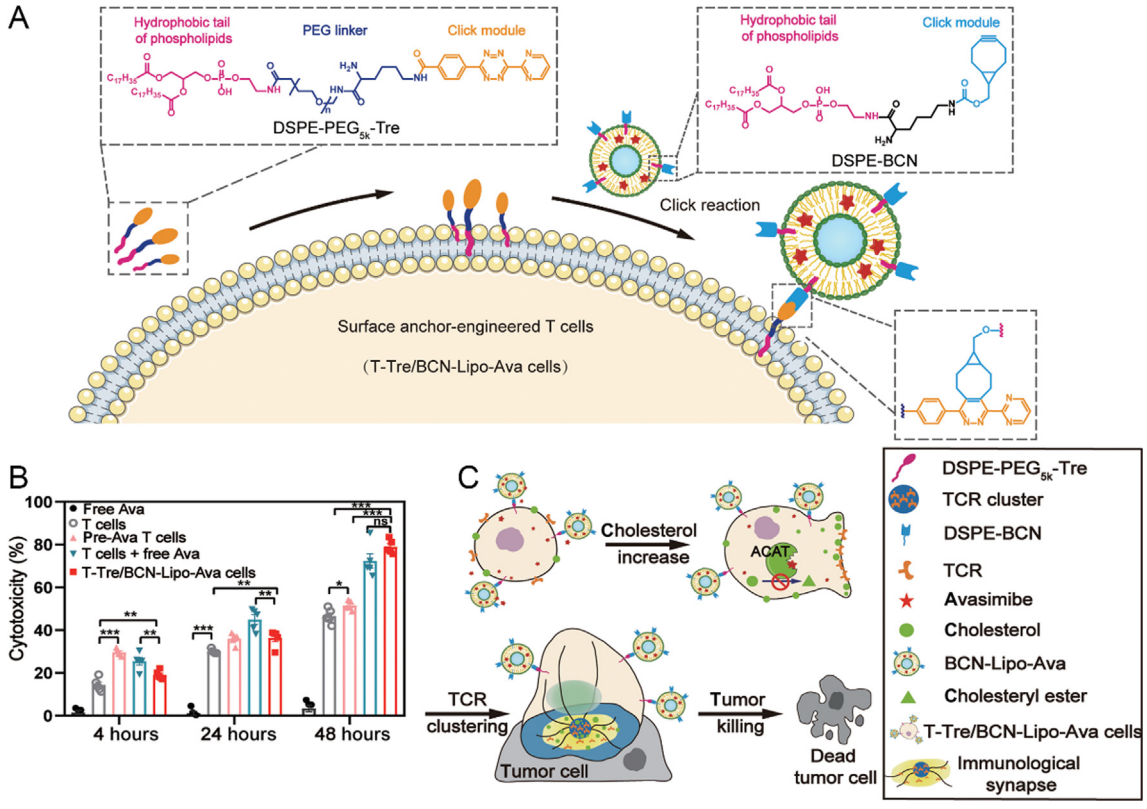

Fig. 4. T cell-based vehicles loading with liposomal avasimibe. (A) Schematic illustration of cell-surface anchor-engineered T cells (T-Tre/BCN-Lipo cells). (B) Cytotoxicity against B16F10 tumor cells. (C) Mechanism of T-Tre/BCN-Lipo-Ava cells for tumor elimination. Reprinted with permission from [104].

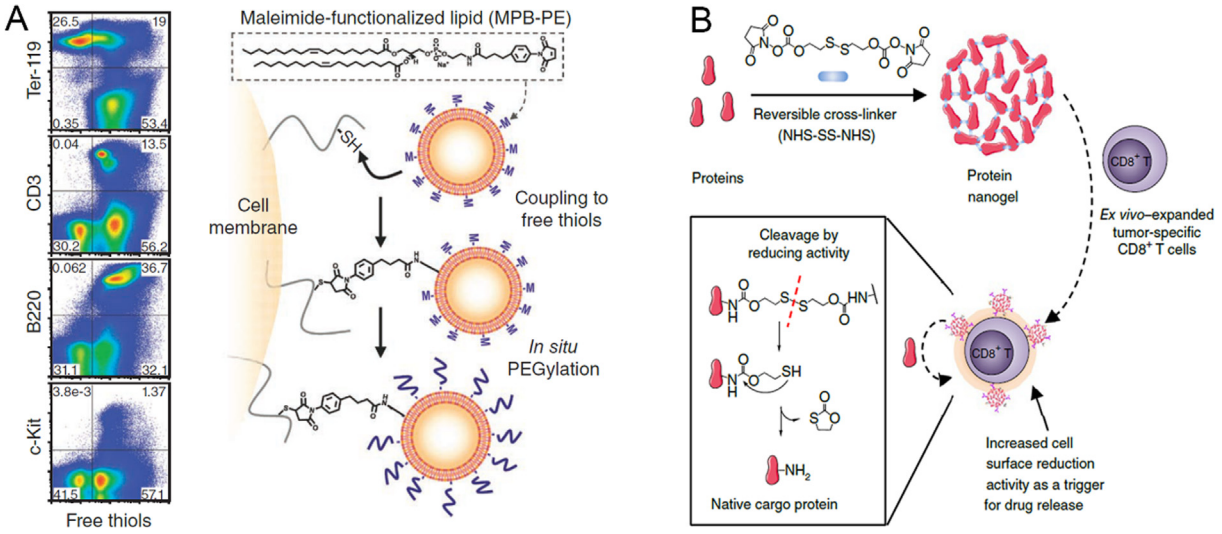

Fig. 5. Schematic illustration of T-cell based vehicles loaded with liposomal cytokines (A) and nanogel cytokines (B). Reprinted with permission from [105].

cyto-pharmaceuticals migrated into both primary and metastatic tumors, unloaded the cargoes to efficiently kill tumor cells. The consequently generated tumor-associated antigens (TAAs) elicited the antitumor immune responses to further suppress the primary and metastatic tumor. In addition, the generated TAAs primed the macrophage vehicles into antitumor M1 phenotype. This study not only exploited the intracellular space of macrophages as the vehicles of two synergistic therapeutics, but also the intrinsic anti-tumor potential.

In the reported work of Qi et al., E-selectin-modified thermal-sensitive micelles were co-loaded with the chemotherapeutic DOX and the A2AR antagonist SCH 58261. After and intravenous injection, they hijacked the circulating leukocytes to cross various biological barriers and achieved increased tumor accumulation, compared with corresponding nanomedicines [111]. In response to the local microwave stimulation, the thermal-sensitive micelles in tumor site released DOX and A2AR. The released DOX killed tumor cells in an immune-cell-death way, provoking anti-tumor immune responses. While A2AR relieved the immunosuppression in solid tumor, which in turn enhanced the anti-tumor cellular immunity provoked by DOX.

In summary, the leukocyte-based drug delivery has been widely used in chemo- photothermal-/phodynamic- or immuno- solid tumor therapy, where researchers have taken full advantages of the inherent tumor tropism of leukocytes. However, the complex and immunosuppressive microenvironment of solid tumor may impede the chemotaxis efficiency of leukocytes to some extent.

5.2. Recruited by amplified inflammation signals

Certain therapies, including surgery, PTT/PDT, and radiotherapy, can induce acute inflammation in residual tumor, which provide amplified inflammation signals to recruit more leukocyte-based vehicles than untreated tumors.

Surgery-mediated recruitment. Taking the post-surgical glioma as the example, our group pioneered the utilization of neutrophil cyto-pharmaceutical of liposomal PTX (PTX-CL/NEs) to target the post-surgical glioma [98]. The gradient inflammatory factors guided the chemotaxis of the PTX-CL/NEs into injured brain glioma, and triggered the release of liposomal PTX from the NEs via the formation of NETs (Fig. 6A). The amount of PTX in residual tumor delivered by neutrophil-based vehicles exhibited about 1000 times as much as that of free PTX, and 85 times more than that of liposomal PTX, thus significantly suppressing the recurrence of glioma in mice. Similarly, Wu et al utilized the NEs loaded with doxorubicin-containing magnetic mesoporous silica nanoparticles (ND-MMSNs) to simultaneously realize a suppression of post-surgical glioma recurrence and an accurate magnetic resonance (MR) imaging (Fig. 6B) [100].

PTT/PDT therapy-mediated recruitment. Light-activated, photosensitizer-based PTT/PDT have been established as safe anti-tumor modalities. However, due to the shallow light penetration depth, these two therapies are known to suffer from tumor recurrence, resulted from the incomplete eradication of microtumors. While, the heat/reactive oxygen species generation in the tumor tissue could induce an acute inflammation, which benefits the recruitment of leukocyte-based vehicles. For example, after gold nanorods-mediated photothermal therapy, the subcutaneous liver tumor exhibited severe tumor necrosis, accompany with the release of inflammatory factors such as IL-8 [119]. The amplified inflammation signals made large amounts of neutrophil cyto-pharmaceuticals of liposomal PTX move to the tumor tissue, achieving synergistic antitumor action with PTT.

In addition to leukocyte cyto-pharmaceutical, the leukocyte-hijacking strategy has also been explored to act as the complementary therapy of PTT. For instance, Li et al. reported a nano-pathogenoid (NPN) system containing cisplatin that can hijack circulating neutrophils after PTT [97]. They found the amount of cisplatin delivered by NPN in the residual tumor was doubled compared to that of traditional NPs-depending on EPR effect. The enhanced accumulation of cisplatin into post-PTT residual tumor mediated by NPN led to a complete inhibition of tumor recurrence.

Radiotherapy-mediated recruitment. Radiotherapy can not only kill tumor cells, but also disrupts the tumor microenvironment and causes radiation-induced inflammation. Our group isolated human circulating neutrophils to internalize the commercial Abraxane (albumin-bound PTX) [120]. The obtained neutrophil cyto-pharmaceuticals of Abraxane were intravenously injected into gastric tumor-bearing mice when the radiotherapy pre-treatment induced inflammation was at its severest stage (characterized by the highest level of inflammatory chemokines in circulation). As a neoadjuvant chemotherapy of radiotherapy, the neutrophil cyto-pharmaceuticals of Abraxane realized a preferable effects on inhibiting tumor growth than Abraxane, due probably to the enhanced PTX delivery efficiency.

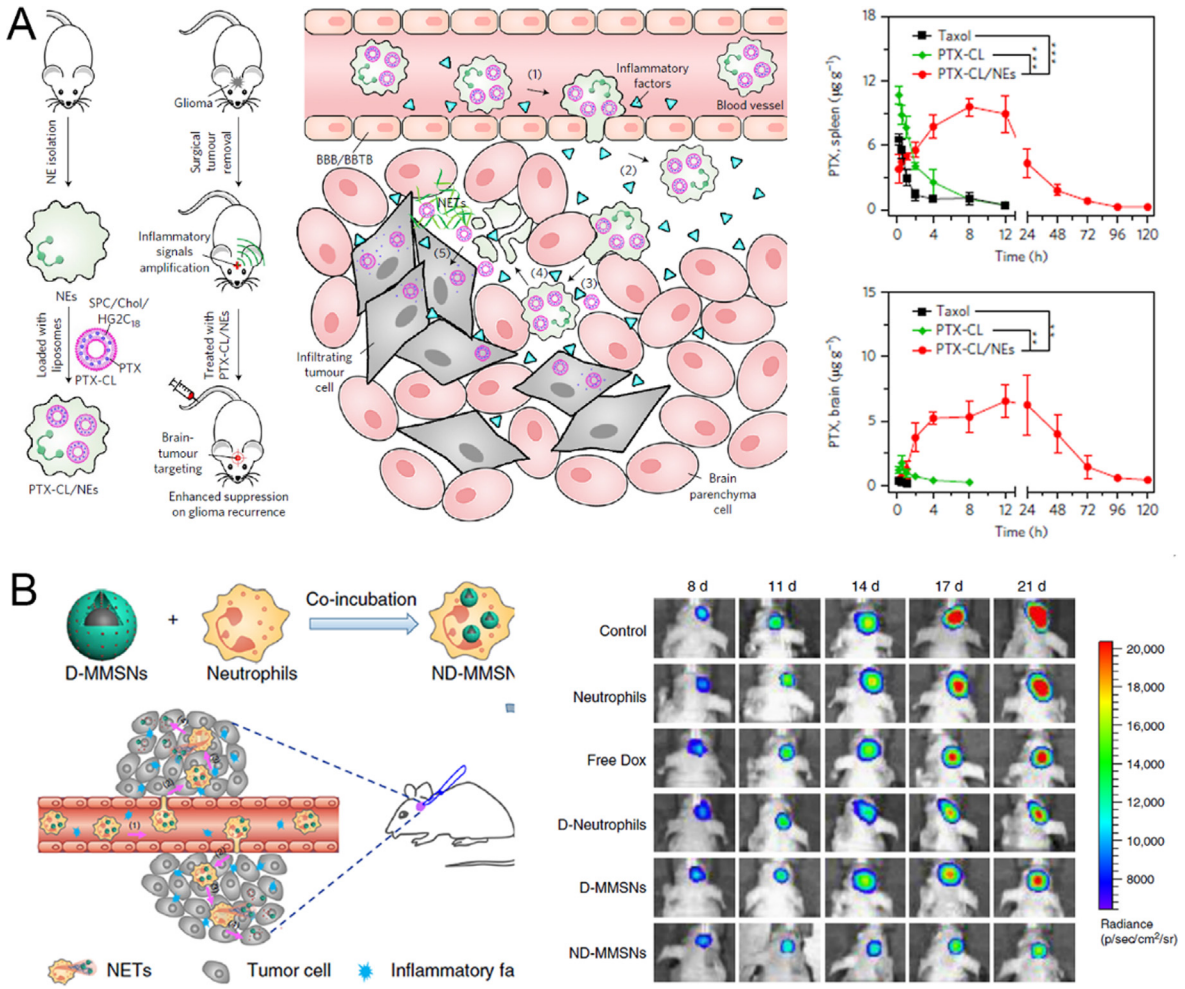

Fig. 6. Neutrophil-based vehicles for suppression of post-surgical tumor recurrence. (A) Schematic design of PTX-CL/NEs for the suppression of postoperative glioma recurrence and quantification of the drug distribution. Reprinted with permission from [98]. (B) Schematic design of ND-MMSNs for accurate magnetic resonance (MR) imaging and residual tumor clearance, and the *in vivo* bioluminescent images. Reprinted with permission from [100].

Taken together, transforming the disadvantages, i.e. acute inflammation, of pre-treatments into the benefits for recruiting leukocyte-based vehicles, could yield the promising synergistic anti-tumor efficacy. However, the influence of pre-treatments on the viability of leukocytes as well as the administration time of leukocyte-based vehicles should be taken into careful considerations.

6. Conclusion and perspectives

Based on a deep understanding of characters of both leukocytes and therapeutics, ingenious and tailored technologies are developed to construct leukocyte-based vehicles, which can actively accumulate towards tumor in an EPR-independent manner. In specific, leukocyte-based vehicles actively migrate across the endothelial barrier (vessel wall) and crawling inside the tissue interstitium in a deformable manner to travel throughout solid tumor.

Despite the promising results obtained in pre-clinic studies, the development of this paradigm-shifting delivery vehicles is still in the initial stage with many challenges: i) the interplay between the carrier leukocytes and loaded cargos should be revealed in detail. For example, how the nanomedicines interact with the abundant enzymes inside carrier leukocytes might decide the stability of leukocyte-based vehicles, especially in the scenario of the "loading into" strategies; ii) facile, benign and efficient cargo-loading technologies to yield intact and robust leukocyte-based vehicles with higher loading efficiency are still in great need. That might involve the development of novel biorthogonal chemistry and safer nano-carriers, optimization of loading methodology, etc; iii) cargo-releasing models of leukocyte-based vehicles are also worth further study; iv) uncertainty of carrier leukocyte phenotype, which might on one hand negatively impact the therapeutic efficacy of leukocyte-based vehicles, on the other hand, provide a window to augment the therapeutic efficiency. That is, we could develop suitable nanotechnology to rationally manipulate phenotype of carrier leukocyte into anti-tumor ones, thus synergistically combing with the efficiency of delivered cargos.

In conclusion, the leukocyte-based vehicles-independent of EPR effect revolutionize the field of drug delivery and hold great perspectives in clinic translation. We kindly believe, with close cooperation among chemists, biologists, clinicians and engineers, tumor patients would benefit a lot from the leukocyte-based vehicles in a clinic-related way.

Declaration of Competing Interest

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

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