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Advances in drug delivery systems utilizing blood cells and their membrane-derived microvesicles

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ABSTRACT

The advancement of drug delivery systems (DDSs) in recent decades has demonstrated significant potential in enhancing the efficacy of pharmacological agents. Despite the approval of certain DDSs for clinical use, challenges such as rapid clearance from circulation, toxic accumulation in the body, and ineffective targeted delivery persist as obstacles to successful clinical application. Blood cell-based DDSs have emerged as a popular strategy for drug administration, offering enhanced biocompatibility, stability, and prolonged circulation. These DDSs are well-suited for systemic drug delivery and have played a crucial role in formulating optimal drug combinations for treating a variety of diseases in both preclinical studies and clinical trials. This review focuses on recent advancements and applications of DDSs utilizing blood cells and their membrane-derived microvesicles. It addresses the current therapeutic applications of blood cell-based DDSs at the organ and tissue levels, highlighting their successful deployment at the cellular level. Furthermore, it explores the mechanisms of cellular uptake of drug delivery vectors at the subcellular level. Additionally, the review discusses the opportunities and challenges associated with these DDSs.

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1. Introduction

The development of drug delivery systems (DDSs) represents a significant milestone in the field of therapeutic technology, with the potential to transform the administration of drugs, particularly those used in cancer treatment (Banerjee & Robinson, 1991; Anselmo & Mitragotri, 2014; Kambale et al., 2022; Syed et al., 2023). By enhancing the efficacy of these medications and improving targeted delivery mechanisms, DDSs are instrumental in reducing systemic toxicity. This enhancement improves the safety profile of treatments, making it a critical technology for addressing a wide range of diseases, including cancer, vascular disorders, and viral infections. The incorporation of drugs with adjuvant compounds in these systems has allowed for augmented therapeutic outcomes in both human and veterinary medicine.

As the focus on this field intensifies, DDSs continue to evolve, driving the exploration of innovative methods and integration with other scientific disciplines. This has resulted in the identification of a multitude of novel possibilities (Laffleur & Keckeis, 2020; Garg et al., 2024; Han et al., 2024; Lei et al., 2024). Despite the growing interest in the clinical use of DDSs, several challenges, such as rapid clearance from circulation, toxic accumulation in the body, and inefficient targeted delivery, continue to impede their successful clinical application. In recent years, the development of materials science and nanotechnology has led to the creation of numerous DDSs based on materials and nanoparticles (NPs) (Wu et al., 2019; Martin et al., 2024; Rarokar et al., 2024; Udofa & Zhao, 2024). Among these, blood cell-based DDSs have emerged as a promising drug delivery strategy due to their low immunogenicity, high biocompatibility, and good stability (Sotiropoulou et al., 2006; Muzykantov, 2010; Villa et al., 2016; Thanuja et al., 2018; Zhang et al., 2021b; Li et al., 2021b; Zhang et al., 2024). To facilitate comparison, we perform a comparative analysis of blood cell-based DDSs in relation to other emerging drug delivery technologies, as illustrated in Table 1. Our analysis centers on various key factors, including targeting ability, biocompatibility, drug payload capacity, and feasibility for clinical applications.

Blood cells, also referred to as 'hematocytes', encompass a variety of cells distributed throughout the body via the bloodstream (Secomb, 2017). In mammals, these cells are primarily composed of red blood cells (RBCs), white blood cells (WBCs), and platelets. Their distinctive anatomical and cellular attributes render them particularly well-suited for drug delivery roles, with RBCs and platelets exhibiting considerable potential in this regard (Nguyen et al., 2023). For example, RBCs are characterized by their distinctive biconcave disk shape and typically range in diameter from 7 to 8 micrometers. This particular shape endows the cells with elasticity and

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Table 1. Comparison of blood cell-based DDSs with other emerging drug delivery technologies.

Factors	Blood cell-based DDS	Nanoparticle-based DDS	Liposome-based DDS	Viral vector-based DDS
Targeting ability	Intrinsic targeting (WBCs, platelets); passive (RBCs)	Surface modification enables targeting	Modifiable for enhanced targeting	High specificity, dependent on viral tropism
Biocompatibility	High inherent biocompatibility	Varies (depends on material)	Generally high, but variable due to composition	Generally high, but can be immunogenic
Drug payload capacity	Moderate; depends on blood cell type	High; wide range of payloads	Moderate to high, efficient encapsulation	High for gene therapy but limited for small molecules
Circulation time	Long (RBCs), moderate (WBCs, platelets)	Extended with PEGylation	Moderate, extendable with PEGylation	Variable, typically short
Stability	High in circulation	Generally high, but sensitive to degradation	Good; enhanced with surface modifications	Stable but sensitive to immune clearance
Manufacture ease	Complex due to biological nature of cells	Rational design and scalable	Complex but well-established processes	Challenging, it requires specialized facilities
Clinical translation	Emerging, with encouraging preclinical results	Advanced; some approved products	Several products on market	Limited, but growing interest in gene therapies
Applications	Cancer, inflammation, cardiovascular diseases	Cancer, infectious diseases, vaccines	Cancer, infectious diseases, genetic disorders	Genetic diseases, cancer therapies

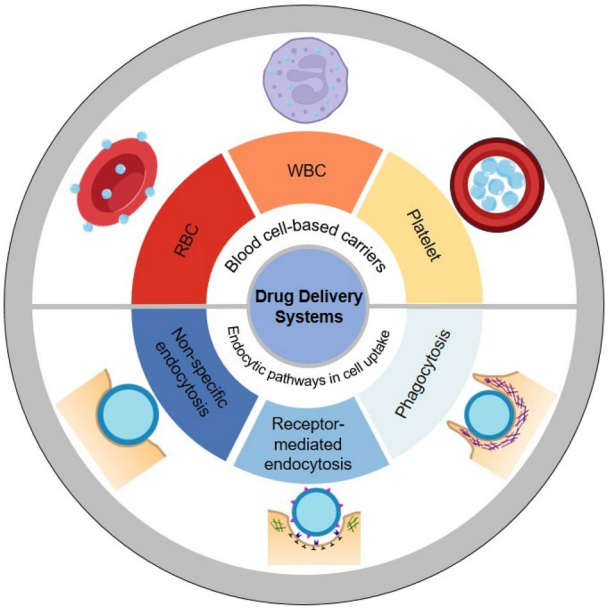

Figure 1. Schematic illustration of blood cell-based drug delivery systems and endocytic pathways involved in cellular uptake of drug delivery vectors.

plasticity, enabling them to alter their shape as needed when navigating through the microcapillary networks. With a lifespan of up to 120 days, RBCs provide a stable and long-lasting vehicle for drug delivery (Zhang et al., 2021a). The absence of genetic material in RBCs reduces the likelihood of immune system targeting, which presents a significant advantage in pharmaceutical applications. Furthermore, specific protein markers on their cellular membranes enable the RBCs to instinctively home in on diseased areas, thereby enhancing the precision of drug delivery (Millán et al., 2004). As nucleus-containing spherical cells, WBCs are larger than RBCs and possess the capacity for deformation, which can be leveraged for a range of drug delivery mechanisms. Given their intrinsic immune functions and ability to adapt to various environmental conditions within the body, WBCs represent an intriguing platform for immunomodulatory treatments. Derived from the cytoplasm of bone marrow megakaryocytes, platelets lack nuclei but possess complete cell membranes and perform vital functions in hemostasis and blood coagulation. Their capacity to form irregular projections upon mechanical or chemical stimulation underscores their potential as DDSs. Their small size and distinctive biconvex shape facilitate navigation of complex bodily environments and intravenous delivery of therapeutic agents.

Blood cells offer a number of notable advantages with regard to their use as drug carriers, both in term of their mechanistic properties and their functional capabilities. Their capacity to remain in circulation for extended periods without triggering an immune response is unparalleled. Furthermore, these cells can be readily obtained from donors, loaded with drug compounds, and reintroduced into patients with minimal risk of triggering adverse immune responses (Ho-Tin-Noé et al., 2011; Mitchell & King, 2015). The intrinsic biodegradability of these carriers ensures that they are naturally metabolized within the body, thereby avoiding the complications associated with synthetic carriers (Pierigè et al., 2008; Wang et al., 2022a).

In recent years, research has expanded to encompass the use of blood cell membrane-derived microvesicles. These micro-sized vesicles retain the parent's biocompatibility and functional properties while presenting easier manipulability at the nanoscale level. Their potential to cross physiological barriers and deliver drugs to otherwise inaccessible locations within the body can significantly enhance therapeutic outcomes. In this review, we will briefly introduce the development of drug delivery systems utilizing blood cells and their membrane-derived microvesicles (Figure 1).

2. Discussion

2.1. Blood cell-based DDSs

2.1.1. RBC-based DDSs

The RBCs are the most abundant blood cells in the human body and have been the subject of considerable research interest as a natural carrier for a range of therapeutic agents in disease treatment and diagnosis (Villa et al., 2016, 2017; Que et al., 2019; Liu et al., 2020). A variety of techniques, including internal encapsulation, external attachment, and physical adsorption, have been employed to leverage intact RBCs as effective drug carriers (Villa et al., 2016, 2017). The internal encapsulation method entails the transient opening of pores on the RBC

membrane, thereby facilitating the entry of large molecule drugs. This process affects cellular integrity and reduces cell lifespan, as well as drug circulation within the body. The external attachment of drugs to RBCs minimizes the impact on the RBC membrane but may result in premature clearance by macrophages, thereby increasing drug toxicity in organs such as the liver and spleen (Shi et al., 2014). Physical adsorption of NPs onto the RBC membrane provides a means for drug transport, enhancing drug delivery efficiency to target tissues by exploiting the squeezing deformation of RBCs in narrow capillaries (Brenner et al., 2018) (Figure 2A).

The use of RBCs loaded with NPs in drug delivery has demonstrated notable enhancements in drug kinetics and efficacy, with considerable potential for targeted drug delivery to specific tissue sites (Figure 2B). For example, the adsorption of NPs on RBCs has been the subject of extensive study, demonstrating that surface modifications of particles can influence their adhesion to the RBC membrane and prevent rapid clearance by macrophages, thus prolonging NP circulation time in the body (Anselmo et al., 2013; Brenner et al., 2018). It is noteworthy that these novel RBC drug carriers have been demonstrated to enhance drug absorption rates in organs such as the lungs and brain, thereby illustrating their potential for the treatment of conditions such as acute stroke and the improvement of drug concentration at specific tissue sites.

In contrast to normal tissues, the microvessel size and branching in tumors are aberrant, creating a distinctive microenvironment conducive to tumor growth and dissemination. However, this also impacts the efficacy of certain cancer treatments. In contrast, the use of RBC carriers for NP drugs in tumors exploits the aberrant vascular branching network within tumors, facilitating precise and targeted drug delivery to tumor sites. Consequently, this method has considerable potential for application and has become a cutting-edge topic among researchers in this field (Anselmo et al., 2013; Wibroe et al., 2017; Brenner et al., 2018; Zhao et al., 2019). For example, research on the physical adsorption of NPs on RBCs has revealed the potential to extend NP circulation time and optimize drug delivery to enhance treatment efficacy (Wibroe et al., 2017). An understanding of factors such as NP size, concentration, and surface modifications can further influence NP adsorption behavior on the RBC membrane, which in turn impacts drug delivery effectiveness (Anselmo et al., 2013; Wibroe et al., 2017; Brenner et al., 2018; Zhao et al., 2019).

The utilization of RBC systems as a unique drug carrier system has the potential to significantly enhance drug kinetics, improve efficacy, and regulate the body's immune response to loaded drugs. Consequently, a multitude of biotechnology companies, including Erytech, Erydel, and Anokion, are engaged in the development of RBC-based drug carrier technologies. Clinical trials have demonstrated the efficacy of RBC-loaded drugs in the treatment of diverse conditions, including ataxia-telangiectasia, Crohn's disease, and leukemia (Li et al., 2021a). For example, in a clinical trial, RBCs loaded with dexamethasone (DEX) were found to alleviate neurological symptoms in patients with ataxia-telangiectasia while avoiding the side effects of DEX (Chessa et al., 2014). Castro et al. employed RBC delivery carriers with DEX to treat 18 children with Crohn's disease and observed a notable reduction in intestinal inflammation and steroid dependence (Castro et al., 2006, 2007). Another clinical trial demonstrated that the use of RBC drug delivery carriers completely avoided the side effects of steroids and could potentially supplant oral steroid treatment for inflammatory bowel disease (Bossa et al., 2013). Additionally, RBC carriers loaded with DEX have anti-inflammatory effects and can be used to treat cystic fibrosis and chronic obstructive pulmonary disease (Lucidi et al., 2006; Rebeyrol et al., 2012). L-asparaginase (L-ASP) is a pharmaceutical agent utilized in the treatment of acute lymphoblastic leukemia; however, its efficacy is constrained by the occurrence of allergic reactions and the diminished enzyme activity observed in certain individuals. It has been demonstrated that L-ASP-loaded RBC drug carriers have exhibited safety and efficacy in patient treatment in clinical trials (Hunault-Berger et al., 2015). The combination of L-ASP-loaded RBC carriers with pancreatic cancer chemotherapy drugs has been demonstrated to significantly extend patient survival (Hammel et al., 2020). A deficiency of adenosine deaminase (ADA) and thymidine phosphorylase (TP) can result in metabolic stagnation and the accumulation of metabolites, which may lead to the development of severe immune disorders (Yadak et al., 2019; Grunebaum et al., 2020). Currently, enzyme replacement therapy (ERT) is regarded as an effective treatment method (Bonam et al., 2019); however, it is constrained by distinctive limitations, namely enzyme degradation and the formation of toxic by-products (Liu et al., 2016). Nevertheless, the encapsulation of enzymes within RBCs can address these limitations (Rossi et al., 2016). In comparison to the administration of ADA alone, the use of RBC drug carriers loaded with ADA has been observed to significantly prolong the circulation time of

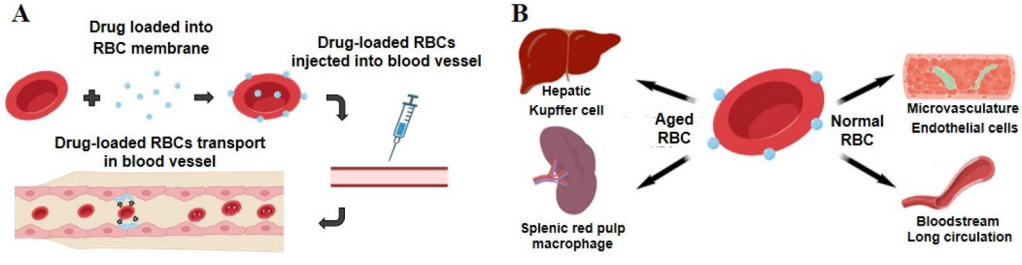

Figure 2. (A) Schematic illustration of the RBC-based drug delivery system designed to transport in vascular systems. (B) Application of the RBC-based drug delivery systems for a range of diseases.

the drug within the body, thereby greatly alleviating disease symptoms in patients (Bourgeaux et al., 2016). In addition, in a clinical trial for mitochondrial neurogastrointestinal encephalopathy, TP-loaded RBC carriers demonstrated a longer half-life, excellent therapeutic effects, and no adverse reactions (Bax et al., 2019).

Irrespective of the method used for drug loading, it is of the utmost importance to conduct a comprehensive evaluation of the pharmacokinetic properties and immunogenicity of drugs that have been attached to RBCs. This is particularly crucial when a significant quantity of drugs have been conjugated to the RBC surface. RBCs, along with their cargo, encounter limitations in penetrating tissue barriers and can only engage with a fraction of the molecules present in the plasma. Furthermore, the presence of numerous molecules on the RBC surface can impact the RBC's half-life, potentially rendering the quantity of nanoparticles bound to the RBC surface insufficient to induce a therapeutic response. Modifications to the cell membrane composition may have deleterious effects on RBC membrane integrity, further complicating their clinical applications. Consequently, the clinical utility of RBC-based DDS remains significantly constrained. Ongoing research endeavors are poised to advance the refinement of RBC drug-loading technology, aiming to broaden the scope of RBC-based drug carriers and expedite their integration into clinical practice.

2.1.2. WBC-based DDSs

WBCs are pivotal immune cells implicated in a range of conditions, including tumors, infections, and immunity. In addition to their role in circulation, WBCs possess distinctive attributes that render them well-suited for drug delivery applications (Che et al., 2020; Chen et al., 2022; Sheu & Hoffmann, 2022). Research on WBC-based DDSs is currently a significant area of focus, with neutrophils and macrophages emerging as promising carriers for therapeutic agents (Figure 3A).

Neutrophils, the primary responders of the immune system, have demonstrated considerable potential in delivering drugs to inflammation sites and overcoming physiological barriers, resulting in notable therapeutic outcomes. These immune cells display an exceptional capacity to migrate to damage sites and actively regulate inflammatory responses when pathogens invade the body (Chu et al., 2018). The utilization of the distinctive attributes of neutrophils for the development of targeted drug carriers represents a promising avenue of research in the field of modern medicine. For example, Xue et al. employed the innate inflammatory homing of neutrophils and their capacity to traverse the blood-brain barrier (BBB) to deliver liposome-encapsulated paclitaxel (PTX), a chemotherapy drug. This resulted in precise and effective drug delivery for glioblastoma treatment post-surgery in murine model (Che et al., 2020). Similarly, Chen et al. demonstrated the efficacy of encapsulating methotrexate (MTX) within neutrophils to form MTX-loaded neutrophils for the treatment of myocardial ischemia-reperfusion injury. This study highlights the potential of this DDS to target inflammatory sites and provide therapeutic benefits. In another study, Ding et al. developed a drug delivery platform using neutrophils by binding them with synthetic sialic acid-lipid conjugates, thereby enabling efficient delivery of doxorubicin liposomes to tumor sites while preserving the cells' intrinsic chemotactic properties (Ding et al., 2021). Furthermore, Dong et al. devised an innovative approach whereby neutrophils were fused with Rvd2 for an ischemic stroke model. This resulted in a marked reduction in inflammation and neural damage (Dong et al., 2019). Another study by Zhou et al. demonstrated that combining cell-loaded NPs with neutrophils facilitated passage through the blood-pancreas barrier, leading to decreased levels of amylase and pancreatic myeloperoxidase, consequently reducing inflammatory responses (Zhou et al., 2019). Collectively, these examples illustrate the significant potential of utilizing neutrophils as drug carriers for targeted therapeutic interventions, demonstrating their versatility and efficacy in addressing a range of inflammatory conditions.

Macrophages are integral elements of the body's immune system, serving as the primary line of defense against pathogens (Sheu & Hoffmann, 2022). Macrophages can be classified into two main types: inflammatory macrophages (M1 type),

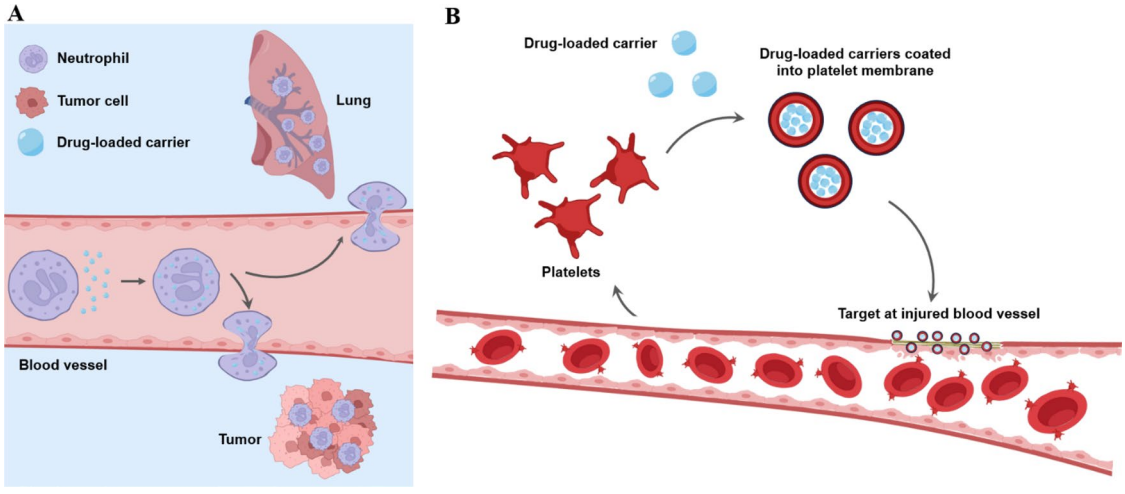

Figure 3. (A) Schematic illustration of a neutrophil-based drug delivery system designed to deliver nanodrugs across the blood vessel barrier. (B) Schematic illustration of platelet-based drug delivery system designed to deliver nanodrugs to target injured sites.

which promote inflammation and eliminate tumors, and anti-inflammatory macrophages (M2 type), which play a role in tissue repair and anti-inflammatory responses (Yunna et al., 2020; Hu et al., 2021). The distinctive receptors present on the membrane of macrophages enable them to interact with specific targets, thereby making them effective carriers for drug delivery to target sites. It has been demonstrated that macrophages can be employed as drug carriers by encapsulating NPs with specific properties into these immune cells, thereby facilitating targeted drug delivery to sites of inflammation, such as tumors (Thamphiwatana et al., 2017; Li et al., 2019a). For example, Gao et al. demonstrated the efficacy of utilizing M2 macrophages loaded with NPs exhibiting ROS-responsive properties to target inflammatory sites with precision and leverage their anti-inflammatory capabilities to treat conditions such as atherosclerosis (Gao et al., 2020). Similarly, Zhu et al. introduced a novel extracellular adhesive NP-macrophage DDS, which provides a platform for developing efficient DDSs based on live cells. This approach maintains macrophage activity and enhances tumor-targeted chemotaxis (Zhu et al., 2023).

A variety of innovative approaches have been explored to enhance drug delivery using macrophages. These include the combination of macrophages with liposomes for the treatment of breast cancer and the targeting of drugs to tumor sites in diseases such as glioma and Parkinson's disease (Batrakova et al., 2007; Madsen et al., 2015; Cao et al., 2016; Rao et al., 2017). For example, Cao et al. combined macrophages with liposomes to deliver emtansine, a drug for breast cancer, which resulted in a notable enhancement in drug delivery to metastatic sites compared to liposomes alone, thereby improving the efficacy of drug treatment (Cao et al., 2016). Additionally, studies examining the potential of macrophages in glioma and Parkinson's disease treatment have yielded encouraging outcomes, particularly with regard to the targeted delivery of drugs to specific disease sites (Batrakova et al., 2007; Madsen et al., 2015).

2.1.3. Platelet-based DDSs

Platelets are small pieces of cytoplasm shed from the mature macrophages. In general, platelets have a lifespan of approximately 8-10 days (Semple et al., 2011), which is considerably shorter than that of RBCs. However, they possess a high storage capacity and are capable of carrying a variety of substances. Platelets patrol the human vascular system, detecting and repairing leaking blood vessels. This makes them ideal candidates for targeting damaged areas and releasing drugs. Furthermore, platelets play a pivotal role in hemostasis, thrombus formation, and inflammation. They are also associated with the growth and metastasis of cancer and wound healing (Roweth & Battinelli, 2021). Consequently, in addition to passive targeting (such as RBC-based DDSs), platelet-based DDSs also demonstrate active targeting due to the distinctive hemostasis-related molecules present on the surface of platelets. In light of these characteristics, a number of platelet delivery systems have emerged (Figure 3B).

In the context of stroke, myocardial infarction, and vascular damage resulting from surgical procedures, platelets primary serve a hemostatic function. Inactive platelets that circulate in the bloodstream play a role in maintaining vascular integrity. In the event of endothelial damage to the blood vessels, the platelets are activated and rapidly adhere to the site of injury, forming a plug to seal the leak (Mackman, 2008). Utilizing this characteristic, in a study conducted by Wu et al., they observed that the anti-thrombotic drug IQCA-TAVV adhere to platelet membranes and, upon injection into the bodies of mice, target thrombotic sites, thereby significantly inhibiting thrombus formation (Wu et al., 2018). Furthermore, thrombolytic drugs employ this same mechanism by binding to the surface of platelet membranes, thereby enhancing their thrombolytic function (Huang et al., 2019, 2021). Wang et al. developed a method for delivering drugs to the surface of platelets, anchoring the thrombolytic drug (Arg/uPA) to the platelet membrane using liposomes. This approach increases the targeting and circulation time of the drug without affecting platelet function (Wang et al., 2022b). Furthermore, the drug can inhibit the subsequent aggregation and activation of platelets at the site of vascular injury, thereby preventing recurrent embolism. In addition, prostaglandin E2, which is secreted by tumor cells, activates platelets and releases transforming growth factor-β (TGF-β), which in turn promotes the mesenchymal transformation of tumor cells, thereby facilitating tumor metastasis (Haemmerle et al., 2018). Chen et al. combined magnetic NPs with platelets to target breast cancer with greater precision by leveraging the homing ability of platelets (Chen et al., 2018). Another study demonstrated that encapsulating drugs in platelet cell membranes resulted in the sequential disappearance of the 4T1 metastatic tumor in a mouse model, significantly enhancing efficacy (Jiang et al., 2020).

The development of platelet-based DDSs has lagged behind that of RBC-based DDSs, with the most advanced systems still in the preclinical development phase. Nevertheless, the endeavors of organizations such as Plasfer, PlateletBio, and Cellphire Therapeutics are rapidly advancing to parallel this progress. For example, Plasfer is a startup company whose primary focus is on platelet-based therapy, with a particular emphasis on the use of platelets to deliver nucleic acid drugs. Their platelet transfer technology platform (PTT^{TM}) is capable of efficiently designing human and mouse platelets to transfect a range of genetic materials, including mRNA, siRNA, microRNA, and plasmid DNA, as well as other categories of molecules, with high efficiency. ZCapsule Inc. is another company engaged in research on platelet delivery systems, with a particular focus on the delivery of large molecule drugs, including PD-L1 and CTLA-4 (Wang et al., 2017). The natural targeting characteristics of platelets are employed to facilitate the delivery of drugs to the site of lesions, including the wound following tumor resection, metastatic lesions, and certain autoimmune-related body tissues. Furthermore, the combination of relevant drugs with platelets through physical adsorption or genetic engineering can enhance the targeted delivery of drugs.

2.2. Extracellular vesicles derived from blood cells as DDSs

Extracellular vesicles (EVs) are NPs secreted by cells with a phospholipid bilayer membrane structure (Zhang et al.,

2020a). They are employed in the treatment of various cancers due to their excellent structural stability, outstanding biocompatibility (Zhu et al., 2017), natural transport ability (Alvarez-Erviti et al., 2011), and superior targeting ability (Valadi et al., 2007; Mittelbrunn et al., 2011). Furthermore, they exhibit enhanced therapeutic efficacy compared to traditional nanomedicines (Shazleen Ibrahim et al., 2024). As a promising drug delivery platform, blood cell-derived EVs are already being used in metabolic regulation, inflammation relief, and cancer treatment.

EVs derived from RBCs possess inherent advantages as drug delivery vehicles (Chang et al., 2010; Deng et al., 2018). Firstly, EVs derived from RBCs lack cell nuclei and mitochondrial DNA, thereby reducing the potential for genome-altering effects on the recipient. Secondly, RBCs are the most abundant blood cells in the body, facilitating the preparation of clinical-grade EVs. Thirdly, EVs derived from RBCs are intrinsic components of RBCs, enabling them to circumvent autologous restrictions and exhibit high biocompatibility. The safety of using RBC-derived EVs as drug delivery vehicles for clinical treatment has been substantiated. For example, Zhang et al. demonstrated that RBC-derived EVs can target the liver and accumulate in liver organs, establishing them as a novel biological preparation for the treatment of liver diseases with high clinical translational potential. Following transplantation, RBC-derived EVs can spontaneously enrich the liver without the necessity for artificial modification, thereby achieving liver targeting. Subsequent research by Zhang et al. involved the loading of doxorubicin or sorafenib into RBC-derived EVs, which resulted in the significant inhibition of orthotropic liver cancer growth in mice. Based on the aforementioned experimental results, they proceeded to develop two distinct formulations: RBC-derived EVs coated with microRNA-155 antisense oligonucleotides and RBC-derived EVs coated with docetaxel. These were designed for the treatment of acute liver failure and orthotropic liver cancer, respectively. Moreover, drug-loaded RBC-derived EVs demonstrated no systemic toxicity at effective therapeutic doses, rendering them a highly promising avenue for the treatment of liver-related diseases (Zhang et al., 2020a). Usman et al. developed a novel DDS based on RBC-derived EVs to deliver antisense oligonucleotide Cas9-gRNA (Usman et al., 2018; Perche et al., 2019). The results demonstrated that this DDS exhibited high delivery efficiency and no significant cytotoxicity, thereby outperforming traditional RNA delivery systems. In addition to delivering RNA, RBC-derived EVs can also deliver superparamagnetic iron oxide particles to bone marrow mesenchymal stem cells for magnetic resonance imaging, thereby enhancing the therapeutic efficacy of stem cell treatment (Chang et al., 2010).

EVs derived from WBCs have the capacity to migrate to sites of inflammation, where they can regulate the body's inflammatory responses (Zhang et al., 2020b; Youn et al., 2021; Deng et al., 2023). For example, Gao et al. employed nitrogen cavitation to disrupt neutrophils, thereby producing neutrophil-derived EVs that were produced at a rate ten times greater than that of naturally secreted EVs. As a result, they have the potential for broader clinical applications. Subsequent studies have incorporated piceatannol (an anti-inflammatory pharmaceutical) into neutrophil-derived EVs, demonstrating a marked reduction in lung injury and sepsis induced by LPS (Gao et al., 2017). Furthermore, neutrophil-derived EVs have the capacity to traverse the BBB. For example, Wang et al. loaded docetaxel into neutrophil-derived EVs, which enabled rapid penetration of the BBB and subsequent entry into the brain, facilitating the treatment of glioma. Additionally, animal experiments demonstrated that neutrophil-derived EVs could target brain-infiltrating tumor cells (Wang et al., 2021). Tang et al. fabricated macrophage membrane-camouflaged liposomes (RM-LIPs) and evaluated their efficacy in extending drug circulation time and targeting the injured spinal cord (Tang et al., 2021). The results demonstrate that RM-LIPs reduce the uptake of the NPs by macrophages and prolong circulation time. Liu et al. prepared EVs derived from macrophage membranes and demonstrated that they could accumulate in large quantities and enhance the concentration of SA and NAL at the lesion sites (Liu et al., 2022). Li et al. developed M2-type macrophage-derived EVs containing a plasmid DNA encoding the anti-inflammatory cytokine interleukin-10 (IL-10 pDNA) and the chemotherapeutic drug betamethasone sodium phosphate (BSP). Their research demonstrates that these EVs, when loaded with these therapeutic agents, effectively target and reduce inflammation, presenting a promising approach for the combined treatment of rheumatoid arthritis (Li et al., 2022a). In a subsequent study, they introduced a messenger nanozyme utilizing an innovative therapeutic strategy that merges nanoscale manganese dioxide with macrophage-derived EVs. Their study illustrates that the messenger nanozyme can selectively targeted inflammatory synovitis, resulting in the reduction of joint damage and cartilage injury in a rat model (Jia et al., 2023). Sagar et al. created a new DDS by hybridizing macrophage-derived EVs with liposomes, exploiting the targeting capabilities of macrophages to deliver drugs to tumor tissues. The delivery system exhibited enhanced efficacy in acidic environments, with accelerated drug release, thereby facilitating drug delivery to acidic tumors (Rayamajhi et al., 2019). Furthermore, macrophages demonstrated effective drug delivery capabilities with a range of water-soluble drugs. For example, Haney et al. demonstrated the efficacy of loading hydrophilic DOX and hydrophobic PTX separately into macrophage-derived EVs in a mouse orthotropic triple-negative breast cancer model (Haney et al., 2020). Yuan et al. encapsulated brain-derived neurotrophic factor within macrophage-derived EVs for the treatment of brain inflammation (Yuan et al., 2017). Another study combined poly(lactic-co-glycolic acid) (PLGA) with macrophage-derived EVs to enclose an intelligent silencer, which was used to treat lung inflammation in mice, offering a novel therapeutic approach for allergic diseases (Pei et al., 2021).

In addition to RBC-derived EVs and WBC-derived EVs, the drug delivery system based on platelet-derived EVs has also been the subject of considerable research interest (Kunde & Wairkar, 2021). The construction of a drug delivery carrier based on the physiological characteristics of platelet-derived EVs can effectively circumvent engulfment by the endothelial system, traverse biological barriers, prolong circulation time,

and rapidly locate and release drugs at the intended site. The use of platelet-derived EVs to load a variety of pharmaceutical agents, including small molecular drugs, inorganic compounds, nucleic acid drugs, and drug-loaded NPs, has demonstrated efficacy in the treatment of cardiovascular diseases, inflammation, vascular repair, malignant tumors, and other conditions, making this a highly active area of research. For example, platelet-derived EVs have the capacity to bind to monocytes in the blood, employing the monocyte-targeting properties to target areas of disease. In light of this property, Li et al. devised a DDS based on platelet-derived EVs (Li et al., 2022b). In this system, monocytes differentiate into macrophages, engulfing platelet-derived EVs in inflammatory environments, resulting in the release of microRNA carried by EVs. Macrophages are then differentiated into M2 types, which contribute to the repair of heart injuries. Zhang et al. loaded cyclophosphamide into mature platelet-derived EVs and demonstrated that it effectively disrupted the immunosuppressive function of programmed death-ligand 1 (PD-L1), thereby reducing the postoperative tumor recurrence rate (Zhang et al., 2018). Xu et al. employed platelet-derived EVs loaded with doxorubicin to achieve immune evasion and attenuated effects, thereby enhancing antitumor efficacy (Xu et al., 2017). By leveraging the targeting capabilities of platelet-derived EVs to preserve damaged arterial walls, Wang et al. demonstrated that the use of platelet-derived EVs to load JQ1 (a BET-bromodomain inhibitor) nanoclusters following a rat carotid artery operation could effectively alleviate neointimal hyperplasia while maintaining the capacity for endothelial cell restoration (Wang et al., 2018). This biomimetic DDS, which obviates the need for the implantation of drug-eluting stents, is not only injectable but also exhibits automatic recognition and targeting functions at the site of injury, thereby offering promising prospects for clinical applications.

2.3. Endocytic pathways involved in cellular uptake of drug delivery vectors

Once the NPs or nanodrugs have been released from the delivery carriers based on blood cells and blood cell-derived EVs, they must first be taken up by the target cells for the drugs to be successfully delivered and to exert a therapeutic effect (Figure 4). Given that the action of drug delivery carriers occurs at the cellular level within the body, it is imperative that researchers possess a comprehensive understanding of the interactions between NPs/nanodrugs and cells (Zhang et al., 2015). The diverse range of NPs and nanodrugs exhibits a variety of physical and chemical properties, which consequently result in differing internalization pathways. Numerous experimental evidences indicate that NPs adsorb to the cell membrane and are internalized by the cell via a range of mechanisms (Zhang et al., 2015; Hui et al., 2020; Guo et al., 2021; Chen et al., 2021a). The mechanisms of internalization of NPs by cells are diverse, resulting in a range of outcomes. Consequently, research on the internalization pathways and influencing mechanisms of cell uptake of NPs is of great importance. Here, we present an overview of the internalization pathways and mechanisms of different types of NPs entering the cells.

2.3.1. Nonspecific endocytosis

The internalization of EVs derived from blood cells is a significant challenge due to their digestion by lysosomes containing acid hydrolases. This presents a crucial limitation for the application of blood cell-derived DDSs in drug delivery. For NPs with diameters between tens and hundreds of nanometers, endocytosis is considered the primary pathway for their entry into cells. In contrast, smaller NPs with diameters between a few nanometers rely on the bending and invagination of the cell membrane, allowing them to penetrate the cell membrane independently. Consequently, studying the direct transport of NPs crossing the cell membrane is essential for the design of drug delivery vehicles.

Previous studies have shown that the penetration process of NPs is contingent upon not only the size, shape, and mechanical properties of the NPs themselves, but also the biomechanical properties of the cell membrane and the cooperative interaction between NPs (Zhang et al., 2015). For example, Sun et al. synthesized NPs with varying water content and hardness. They found that rigid NPs are more readily internalized by cells than soft NPs, which undergo deformation during the internalization process, rendering them energetically unfavorable (Sun et al., 2015). Li et al. demonstrated that the hardness of NPs influences their transmembrane endocytic pathway (Li et al., 2015). Ji et al. employed asymmetric modification of the particle surface to regulate the rotational behavior of NPs on the cell membrane (Ji et al., 2016). They observed that when the surface area was coated with shorter or harder ligands, there was a greater tendency for the NPs to interact with the cell membrane. Wang et al. conducted computational simulations to investigate the translocation process of soft NPs with varying elasticities and surface hydrophobicities through a lipid bilayer membrane (Wang et al., 2019). The results demonstrated that the translocation abilities of hydrophilic NPs can be enhanced by increasing their stiffness, whereas the penetrability of hydrophobic NPs is weakened by increasing the particle stiffness. In previous research conducted by Gao's group, it was demonstrated that the particle wrapping process is determined by a balance between elastic energy loss and adhesive energy gain, which results in two distinct ingestion pathways, namely tip-first and side-first pathways. This underscores the significant of particle orientation in determining the pathway (Yu et al., 2018). Furthermore, Yi and Gao conducted a theoretical analysis of the morphological evolution of lipid-membrane-encapsulated elastic rod-shaped NPs (Yi et al., 2011). The study demonstrated that soft, elongated NPs undergo morphological alterations during the process of membrane encapsulation, whereas rigid NPs do not exhibit notable elastic deformation during cell internalization. Yi et al. employed a Lagrange-Euler coupling description to simulate the deformation of linear elastic thin shell capsules and cell membranes using a (Yi & Gao, 2015). Their findings indicated that harder nanocapsules require less adhesive energy to achieve complete encapsulation than soft nanocapsules.

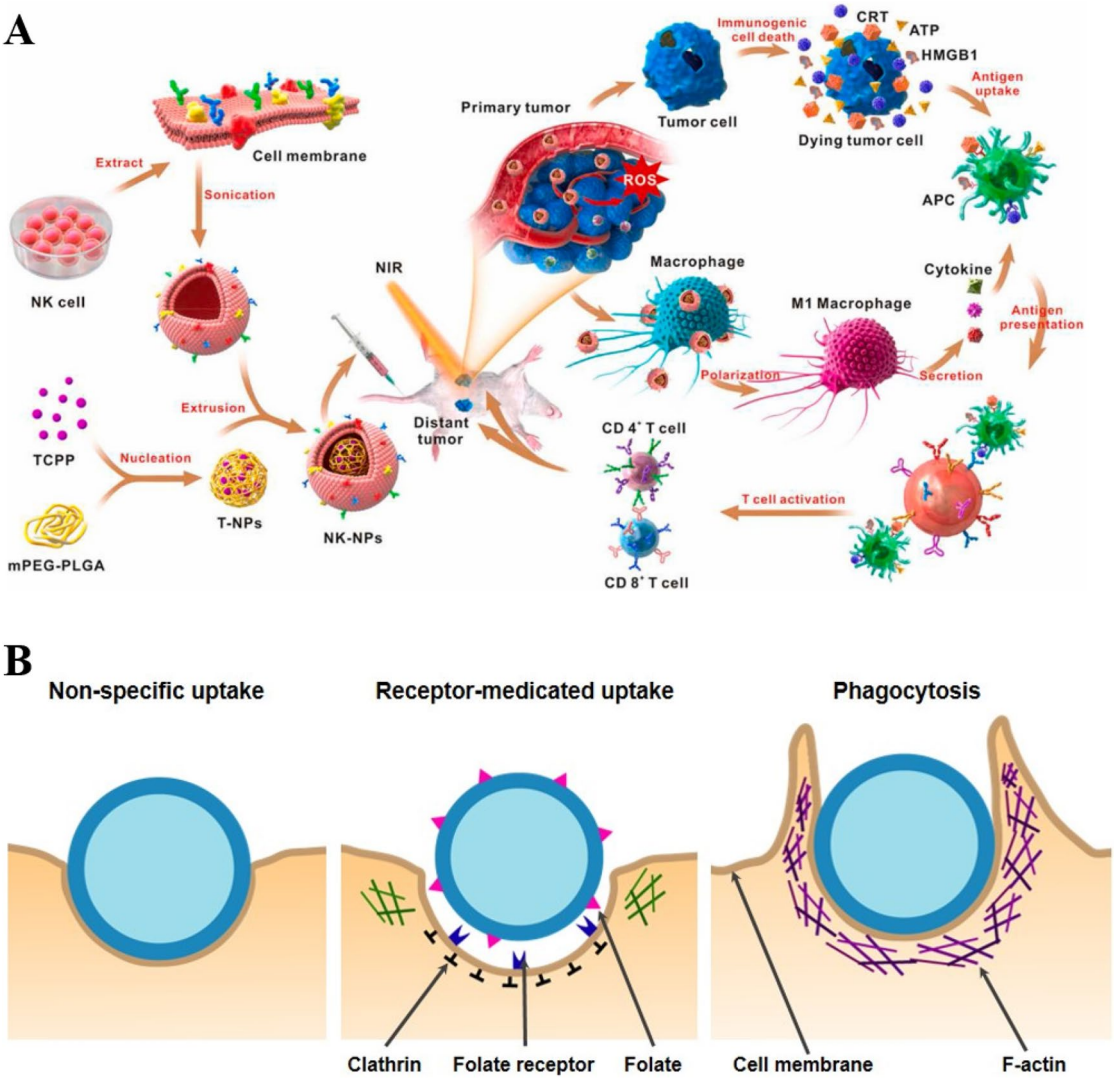

Figure 4. Cellular uptake and retention of drug delivery vectors. (A) Incorporation of NPs into the cell membrane and its illustration in the field of tumor targeting. Reproduced from (Deng et al., 2018) with permission from the American chemical society. (B) Schematic illustration showing the different cellular uptake pathways. Reproduced from (Hui et al., 2020) with permission from AAAS.

Additionally, their study demonstrated that the hardness of NPs significantly affects the efficiency of cell internalization.

The adhesion of NPs to biological membranes results in complex shape deformations, which in turn induce local membrane curvature. This phenomenon gives rise to indirect interactions between the adsorbed materials. This curvature-mediated interaction and the associated membrane remodeling are of great importance in a number of biological processes, including the delivery of NPs encapsulating therapeutic drugs to tumor cells. A comprehensive understanding of the interactions between NPs and cell membranes, and the multi-body interactions that ensure, is of great importance for the development of innovative diagnostic and therapeutic strategies for different diseases. For example, Sarfati and Dufresne employed maximum likelihood estimation to examine the trajectories of NPs on the cell membrane, and their findings indicated that the interactions between particles undergo alterations with increasing particle separation, and are associated with membrane tension (Sarfati & Dufresne, 2016). Koltover et al. found that NPs that are either chemically bound or physically adsorbed onto flexible vesicles can be partially encapsulated and separated into aggregated phases (Koltover et al., 1999). Idema et al. demonstrated that membrane-mediated interactions on vesicles regulate the formation of size-ordered structural domains (Idema et al., 2010). Yan et al. investigated the cooperative effect of wrapping multiple adhesive NPs on both the same and opposite sides of a membrane (Yan et al., 2019). They demonstrate the significance of the magnitude and direction of membrane bending in regulating curvature-mediated NP interactions. Chen et al. conducted a systematic study of how soft NPs wrap around membranes due to curvature and their interactions (Chen et al., 2021b). They discovered that the wrapping pathway depends on the particle size. These studies offer valuable insights into curvature-mediated interactions. The assemblies of NPs on membranes are influenced by curvature and can guide the design of NPs for targeted drug delivery.

The nonspecific cellular uptake of NPs has emerged as an important drug delivery system, with notable advancements in understanding the mechanisms of cellular uptake, the influencing factors, and the advanced technologies involved.

With the ongoing technological innovation and deeper research, it is anticipated that the applications of NPs in drug delivery will become even more diverse and expansive.

2.3.2. Receptor-mediated endocytosis

Receptor-mediated endocytosis refers to the process by which cell surface receptor proteins facilitate the internalization of substances. It is the most prevalent pathway for NPs to gain access to cells. In the context of drug delivery, receptor-mediated endocytosis of NPs refers to the process by which drug molecules bind to specific receptors on the cell membrane, thereby triggering the internalization process and ultimately facilitating the release of drug particles into the interior of the cell. The combination of receptor-mediated endocytosis and suitable nanocarriers allows for the efficient drug delivery and controlled release of drugs, increasing the uptake rate and improving the bioavailability and efficacy of drugs inside the cells. Therefore, this approach has been widely researched and applied in drug delivery.

The process of NPs entering the cells through receptor-mediated endocytosis is a complex biological process, and a number of factors can affect the efficiency and pathways of NPs entering the cells. The process of receptor-mediated internalization commences with the binding of ligands attached to NPs binding to specific receptors on the cell membrane, which initiates a conformational change that results in the formation of a membrane invagination, leading to the development of early endosomes. It is therefore evident that cell surface receptor proteins play a crucial role in the internalization process. The choice and affinity of receptors for binding ligands, as well as the structure and specificity of different receptors, determine the binding mode of drug particles to the cell membrane and the initiation mechanism of internalization. A number of different types of receptors, including G protein-coupled receptors and receptor tyrosine kinases, have been demonstrated to facilitate the internalization of substances. The selection of specific receptors to facilitate the internalization of NPs enables the precise delivery of drugs. For example, the transferrin receptor (TfR) can be employed to facilitate targeted drug delivery to the brain tissue, which is crucial for the treatment of nervous system-related disorders. Ding and Ma studied the impact of chemical and physical characteristics of envelope ligands on the internalization of NPs by cells (Ding & Ma, 2018). Their findings revealed that the strength of the interaction between receptors and ligands, as well as the density, length, and hardness of the ligands, play an important role in regulating the equilibrium of receptor-mediated internalization.

The delivery of drug carriers derived from blood cells through receptor-mediated endocytosis also presents challenges and unresolved issues. For example, there is a need to identify suitable receptors, achieve precise modification of blood cells, and ensure the successful release of drugs during receptor-mediated internalization without being digested by lysosomes. Consequently, a deeper comprehension and further investigation into the subject of endocytic vesicles can facilitate the enhancement of the design and optimization of the DDSs for precise treatment of different diseases.

2.3.3. Phagocytosis

Phagocytosis is the process by which cells absorb and clear particles larger than 0.5 micrometers, including microorganisms, foreign substances, microvesicles, and blood cells. It is a fundamental process of the immune system and plays an essential role in maintaining the cleanliness and immune defense of the body's internal environment. The primary function of phagocytic immune cells, such as macrophages, is to engulf and destroy diseased or dying cells. The process of engulfing apoptotic or dying cells is referred to as efferocytosis.

Researchers have developed an innovative method based on the efferocytosis of phagocytic cells for the creation of DDSs utilizing apoptotic blood cell membranes (Poon et al., 2014; Tang et al., 2022; Zhou et al., 2022). For example, inspired by the targeting and non-immunogenicity of efferocytosis by macrophages, Ma et al. prepared apoptotic endothelial cell membranes for drug delivery, demonstrating that drug delivery induced by cell apoptosis provides a novel pathway for targeted drug delivery using biological regulatory mechanisms (Ma et al., 2002). Furthermore, Sun et al. developed macrophage biomimetic nanomedicines for targeted delivery to the colon, demonstrating excellent targeting and therapeutic effects in the treatment of ulcerative colitis (Sun et al., 2020). Zhao et al. extracted neutrophil membrane vesicles, fused them with liposomes and constructed neutrophil-like NPs that targeted intercellular adhesion molecule-1 in inflammatory colonic sites, thereby relieving colitis (Zhao et al., 2019).

A comprehensive understanding of the interactions between foreign substances and cell membranes during phagocytosis is crucial for elucidating the fate of live cells and for the advancement of biomedical applications, including drug delivery. Prior to the completion of the phagocytosis process, the interaction between the phagocytic cells and particles must be facilitated through adhesion. This is contingent upon the surface chemical properties of the particles in question. Furthermore, the velocity of phagocytic cells in engulfing particles is dependent upon the shape and size of the particles. Studies have demonstrated that the engulfment time of non-spherical particles may be five times longer than that of spherical particles (Paul et al., 2013). It has been observed that discoidal particles are more readily engulfed than spherical particles, and spherical particles are more readily engulfed than ellipsoidal, rod-shaped, or needle-shaped particles (Lu et al., 2010; Sharma et al., 2010). Hui et al. studied the influence of NP elasticity on cell uptake, which is contingent upon the nature of the cell-NP interaction (Hui et al., 2020). They observed that during the process of cell uptake, rigid NPs retained their spherical shape; however, soft NPs underwent deformation due to specific ligand-receptor interactions and membrane wrapping, which resulted in a reduction in their binding and internalization rates with cells. These findings suggest that phagocytosis is a complex, dynamic process involving reorganization of the cell skeleton, deformation of the membrane shape, and aggregation of different proteins (Richards & Endres, 2017).

3. Intricate relationship between blood cell roles, disease relevance, and engineering strategies

Understanding the roles of blood cells in drug delivery requires a confluence of biology, disease pathophysiology, and engineering principles. Blood cells serve as natural components of the body's immune system and can be engineered to serve as vectors for therapeutic delivery, presenting unique opportunities to address specific disease challenges through innovative engineering strategies.

3.1. Roles of blood cells in disease relevance

Blood cells play a vital role in maintaining homeostasis and defending against pathogens. Therefore, their involvement in diseases such as cancer, cardiovascular disorders, and autoimmune diseases can be both ambiguous and potentially exploitable for therapeutic purposes:

- **Cancer:** Blood cells have been found to infiltrate tumors, exerting varied impacts on cancer progression. For instance, tumor-associated macrophages may exhibit pro-tumorigenic behavior. The use of engineered RBCs or platelets to deliver chemotherapeutic agents directly to tumors can take advantage of natural homing mechanisms to enhance drug uptake, especially in hypoxic tumor regions (Mieszawska et al., 2012).
- **Cardiovascular disease:** Platelets and WBCs play a role in inflammation and thrombosis, which are crucial processes in conditions like atherosclerosis or myocardial infarction. Engineered platelets can be employed in targeted DDSs to administer anti-inflammatory or anti-thrombotic medications, potentially improving treatment outcomes while reducing systemic side effects (Wang et al., 2022b).
- **Autoimmune disease:** WBCs are often dysregulated in autoimmune disease, leading to inappropriate immune responses. Leveraging RBCs for the delivery of immunosuppressive drugs can help modulate immune activity without compromising the overall immune response (Nguyen et al., 2023).

3.2. Engineering strategies for blood cell-based DDSs

Various engineering strategies have been developed to harness the potential of blood cells for addressing specific disease challenges (Li et al., 2024):

- **Surface modification:** By modifying the surface of blood cells, scientists can enhance the targeting efficiency and drug-loading capacity. Techniques such as biotin–avidin coupling and EDC/NHS chemistry allow for the covalent attachment of therapeutic agents or targeting ligands to the blood cell surface (Abbina et al., 2018).
- **Encapsulation techniques:** Drugs can be encapsulated within blood cells through techniques such as hypotonic loading or electroporation, which are designed to temporarily increase membrane permeability. This strategy is particularly useful for protecting labile therapeutic compounds from premature degradation or clearance, thereby improving drug delivery efficacy (Li et al., 2019b).
- **Genetic engineering:** While mature RBCs and platelets have limited genetic material, progenitor cell engineering, such as with hematopoietic stem cells for WBCs, could allow for the expression of therapeutic proteins within cell-derived vesicles, expanding the utility of blood cell-based DDSs (Chao et al., 2023; Li et al., 2024).
- **Nanoengineering:** The integration of nanotechnology with blood cell mechanics facilitates the development of hybrid systems like NP-decorated RBCs, which can carry higher drug loads and exhibit improved pharmacokinetics. These hybrid systems can navigate the circulatory system and access sites of disease with improved specificity (Mitchell et al., 2021; Ullah et al., 2024).

In summary, the intersection of blood cells in drug delivery with disease relevance and engineering strategies presents a promising avenue for the development of precise and personalized therapeutic approaches. Ongoing research efforts are focused on refining these strategies to enhance targeting accuracy, minimize side effects, and broaden the scope of treatable diseases.

4. Conclusions

The blood cell-based drug delivery systems (DDSs) utilize specific blood cells, such as red blood cells (RBCs), white blood cells (WBCs), and platelets, as carriers for therapeutic and diagnostic agents. They offer advantages such as biocompatibility, reduced macrophage uptake, prolonged circulation time, and modified distribution within organs and tissues. These characteristics make blood cells and blood cell membrane-derived extracellular vesicles (EVs) promising DDSs for various therapies and biomedical interventions, with significant potential in the treatment of cancer and other diseases. This review focuses on recent advances in the use of blood cells and their membrane-derived EVs as drug carriers, presents different methods for loading drugs onto these blood cells, and reviews different endocytic pathways involved in the cellular uptake of drug delivery vectors. In conducting a comparative analysis, we have compiled a comprehensive table summarizing crucial data on blood cell-based DDSs as outlined in Table 2. The table provides a detailed account of the various blood cell types employed in drug delivery, elucidating their respective characteristics, benefits, challenges, endocytic pathways, and therapeutic impacts. Through the examination of Table 2, distinctive advantages of each strategy in targeting efficiency, circulation longevity, and immune system compatibility become apparent. Choice of the delivery method is contingent upon factors such as the targeted disease, desired therapeutic outcomes, and potential adverse effects. A thorough comprehension of the cellular

Table 2. Summary of the blood cell-based DDSs.

Delivery strategy	Characteristics	Advantages	Challenges	Endocytic pathways	Therapeutic effects	Applications	Outcomes of preclinical / clinical studies
RBCs	High abundance; Long lifespan (120 days in humans)	Biocompatibility; Prolonged circulation	Limited targeting capability	Phagocytosis	Prolonged circulation; Reduced immunogenicity	Suitable for chronic conditions requiring steady-state medication levels, such as enzyme deficiencies or chemotherapy delivery	Enhanced drug bioavailability and reduced side effects in animal models of cancer
WBCs	Intrinsic targeting to inflammation and tumors	High specificity; Natural targeting to inflammation or tumors	Complex isolation and modification; Potential immunosuppression	Phagocytosis	Targeting inflammation; Immune modulation	Effective in treating autoimmune diseases, infections, and certain cancers where immune cells are actively engaged	Targeting of inflammation and tumors in preclinical models; Effective reduction in systemic inflammation in phase II trial
Platelets	Natural role in hemostasis and inflammation	Inherent targeting to vascular injury and tumors	Limited lifespan; Complex storage	Phagocytosis; Receptor-mediated endocytosis.	Home to injured endothelium; Drug stability	Used for targeted delivery in thrombosis treatments, and tumor targeting via chemotherapeutic agents	Improved targeting to thrombi without increasing bleeding risk in murine models
Blood cell-derived EVs	Multiple properties based on the relevant blood cells.	Biocompatibility and low immunogenicity; Natural targeting abilities; Versatile payload capacity	Heterogeneous characteristics; Complex isolation and purification	Nonspecific endocytosis; Receptor-mediated endocytosis; Phagocytosis	Intercellular communication; Barrier penetration	Potential in treating neurological disorders, cancer, and inflammatory conditions, with reduced off-target effects	Early-phase clinical trials have primarily focused on assessing the safety profile of EVs in human subjects. These studies show that EVs are well-tolerated, with minimal incidences of adverse reactions reported

It includes an overview of the different types of blood cells used for drug delivery, detailing their characteristics, advantages, challenges, endocytic pathways, therapeutic effects, and the outcomes of relevant preclinical and clinical research studies.

mechanisms intrinsic to each approach, particularly their endocytic pathways, is essential for the optimization of drug delivery tailored to specific therapeutic needs.

Blood cell-based DDSs demonstrate good biocompatibility and targeting capabilities, positioning them as a promising drug delivery system with potential for clinical applications. However, these systems are still in the early stages of development and face unresolved issues. The use of blood cells as drug carriers, regardless of blood cell types, is currently limited to small-scale applications. Blood cell-based DDSs face several notable challenges that must be overcome to achieve clinical success (Muzykantov, 2010; Anselmo & Mitragotri, 2014). One major challenge is the complexity involved in the isolation and functional modification of blood cells, such as RBCs, WBCs, and platelets (Shi et al., 2014). These processes need to preserve the innate properties of the cells while enabling them to effectively deliver therapeutic agents. Furthermore, the relatively short circulation times of WBCs and platelets limit the duration over which drugs can exert their effects, while modification of RBCs may alter their natural lifespan (Mitchell & King, 2015). Another key challenge is the potential immunogenicity of these systems, particularly when non-autologous cells or significant modifications are used, which can trigger immune responses and reduce the efficacy of the system (Semple et al., 2011; Deng et al., 2018). Additionally, ensuring precise targeting of the drug delivery to specific tissues or disease sites is difficult without specific modifications, as not all blood cells have inherent targeting capabilities (Semple et al., 2011; Li et al., 2022b). Finally, the scalability and reproducibility of these systems for large-scale clinical use remain significant hurdles, compounded by the rigorous standards required for regulatory approval (Li et al., 2024; Zhang et al., 2024).

Several strategies are being developed and refined to address these challenges (Pierigè et al., 2008; Mieszawska et al., 2012; Ullah et al., 2024). To enhance isolation and modification processes, advanced techniques such as microfluidic sorting and non-disruptive drug-loading methods such as electroporation or encapsulation technologies are being used to maintain cell integrity while allowing drug delivery. Surface engineering techniques, such as the application of PEGylation or the incorporation of biocompatible molecules, can help extend circulation times and reduce immune detection, thereby increasing the stability of the modified cells. The use of autologous cells or the application of stealth technologies through surface modifications can mitigate immune response issues, making the system more biocompatible. To improve targeting specificity, researchers are exploring the attachment of targeting ligands or antibodies to cell surfaces, guiding the delivery to specific tissues or disease markers. Additionally, the development of scalable manufacturing processes with built-in quality control systems can enhance the production consistency required for regulatory approval. Through the integration of these strategies, the feasibility and efficacy of blood cell-based DDSs will be significantly enhanced, paving the way for their broader application in precision medicine (Mitchell et al., 2021; Chao et al., 2023; Ullah et al., 2024).

Authors contributions

Andong He: Conception and design of the study; Writing-original draft; Writing - review & editing; Visualization. Yuye Huang: Data gathering and organization; Drawing the Figures and Tables; Writing-original draft; Writing - review & editing. Chao Cao: Conceptualization; Supervision; Writing-original draft; Writing - review & editing. Xuejin Li: Conceptualization; Supervision; Writing-original draft; Writing - review & editing. All authors have read the final manuscript and agree to publish this work.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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