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REVIEW

Advancements in precision nanomedicine design targeting the anoikis-platelet interface of circulating tumor cells

Manqing Tang[a,†], Zhijie Zhang[a,†], Ping Wang[a,†], Feng Zhao[a], Lin Miao[b], Yuming Wang[a], Yingpeng Li[a,*], Yunfei Li[a,*], Zhonggao Gao[c,*]

[a]*College of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China*
[b]*State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China*
[c]*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*

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Abstract Tumor metastasis, the apex of cancer progression, poses a formidable challenge in therapeutic endeavors. Circulating tumor cells (CTCs), resilient entities originating from primary tumors or their metastases, significantly contribute to this process by demonstrating remarkable adaptability. They survive shear stress, resist anoikis, evade immune surveillance, and thwart chemotherapy. This comprehensive review aims to elucidate the intricate landscape of CTC formation, metastatic mechanisms, and the myriad factors influencing their behavior. Integral signaling pathways, such as integrin-related signaling, cellular autophagy, epithelial-mesenchymal transition, and interactions with platelets, are examined in detail. Furthermore, we explore the realm of precision nanomedicine design, with a specific emphasis on the anoikis−platelet interface. This innovative approach strategically targets CTC survival mechanisms, offering promising avenues for combatting metastatic cancer with unprecedented precision and efficacy. The review underscores the indispensable role of the rational design of platelet-based nanomedicine in the pursuit of restraining CTC-driven metastasis.

*Corresponding authors.
E-mail addresses: liyingpeng@tjutcm.edu.cn (Yingpeng Li), liyunfei@tjutcm.edu.cn (Yunfei Li), zggao@imm.ac.cn (Zhonggao Gao).
[†]These authors made equal contributions to this work.
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1. Introduction

The shocking fact is that the majority of cancer deaths, up to 90% of all fatalities, are attributed to metastasis[1]. The intricate process involves the journey from primary tumor inception to successful colonization at distant sites, encompassing detachment from the extracellular matrix (ECM), transition into CTCs[2], traversal of challenges in circulation, and establishment at remote locales. CTCs, which are a subset of tumor cells, are crucial in the spread of cancer and encounter biological barriers at each stage of the process.

Within the orchestrated sequence of cancer metastasis, tumor cells must evade anoikis to establish colonies in distant organs[3]. Anoikis resistance, akin to apoptosis, is crucial for CTCs' persistence in peripheral blood, resisting mechanical stresses, evading immune surveillance, and withstanding chemotherapeutic agents. Cancer cells' anchorage-independent phenotype allows them to endure without adhesion, enabling CTCs to withstand anoikis, a leading factor of cancer-related deaths[4]. Platelets assume a pivotal role in facilitating metastatic spread, notably in anoikis resistance. Their numbers and activation state support CTC survival, enabling them to withstand shear stress and immune attacks[5]. In tumor cells, platelets promote metastasis by instigating epithelial-mesenchymal transition (EMT)[6,7]. Considering their paramount role, interventions targeting platelet function emerge as potent therapeutic avenues against metastasis.

In parallel, nanoparticles offer promise in cancer therapy, enhancing bioavailability, mitigating toxicity, and allowing controlled release[8]. Platelet membrane-based nanoparticles capitalize on platelets' affinity for targeting tumors, offering a versatile arsenal for cancer therapeutics[9]. They provide prolonged circulation times, heightened tumor accumulation, and precise targeting, holding potential as a tenable modality[10].

Thus, understanding anti-anoikis mechanisms and leveraging nanodelivery systems offer avenues for efficacious cancer treatment. The discourse delves into the genesis and mechanics of CTCs, dissecting signaling pathways, autophagy, EMT, and platelet interactions. Breakthroughs in nanomedicines, particularly the anoikis−platelet interface, targeting CTC survival mechanisms, are explored in-depth.

2. Understanding CTC survival dynamics and navigating anoikis challenges

Anoikis, a programmed cell death triggered by the loss of cell−ECM and cell−cell adhesion, serves as a crucial mechanism to prevent inappropriate cell migration and adhesion while promoting tissue turnover. This process becomes particularly pertinent when cancer cells detach from their primary location, transforming into CTCs in the bloodstream. In this state, they encounter anoikis—an apoptosis form triggered by detachment from the extracellular matrix. Despite the inherent challenge, a select subset of CTCs remarkably manages to survive this phase, acquiring the ability to evade anoikis. This survival, particularly within a favorable microenvironment, facilitates their progression into metastasis[11].

CTCs exhibit remarkable resilience against anoikis, a resilience attributed to specific gene modifications and aberrant expression of key molecules within these cells. Alterations in genes governing the cell cycle, such as *TP53* and *PTEN*, play a pivotal role by contributing to unregulated proliferation and enhancing the viability of CTCs. This uncontrolled proliferation is a result of dysregulated cell cycle checkpoints, a hallmark of cancer cells, further underlining the significance of these gene modifications in CTC survival[12]. Moreover, aberrant expression of components involved in apoptosis pathways is a critical factor in conferring resistance to cell death signals, thereby fostering the prolonged survival of CTCs. Notable examples include members of the BCL-2 family, which regulates apoptosis, and inhibitors of apoptosis proteins (IAPs)[13]. These molecular alterations in apoptosis-related elements highlight the intricate mechanisms that CTCs employ to evade cell death, emphasizing the adaptability and survival strategies adopted by these cells within the challenging context of anoikis.

Cancer stem cells (CSCs), a distinct subset within tumor cell populations, are characterized by stem cell features, including limitless proliferation and self-renewal capabilities[14]. This unique phenotype arises from specific genotypic alterations involving key genes such as NANOG, OCT3/4, and SOX2. Concurrently, modifications in molecular phenotypes, such as ICAM-1 and CD133, contribute to the acquisition of CSC-like attributes by CTCs, thereby enhancing their survival capabilities[15]. To identify CSCs within CTCs, biomarkers play a crucial role by underscoring their CSC-like characteristics and providing valuable insights into their survival and metastatic potential. Examples of these biomarkers include CD34, CD44, CD166, ALDH1, and EpCAM. The presence of these markers not only aids in the identification of CSCs within the CTC population but also serves as a window into understanding the unique biological properties that drive the survival and metastatic potential of these cells.

Understanding the intrinsic features of CTCs associated with anoikis is pivotal for unraveling their significance in cancer progression and treatment resistance. Gene modifications and molecular expression patterns within CTCs unveil their potential for uncontrolled proliferation and resistance to apoptosis. Cell cycle regulatory gene alterations and the dysregulation of apoptosis pathways contribute to the remarkable survival capabilities of these cells, emphasizing their role in metastasis and treatment challenges.

3. The evolution of anoikis resistance in cancer metastasis

3.1. Anoikis in CTC survival and metastasis

Anoikis play a pivotal role in safeguarding tissues by initiating apoptosis in cells detached from their primary environment, thereby preventing their survival and migration to inappropriate locations[16]. This process involves activating pro-apoptotic events,

particularly in mitochondria or disk-like structures, leading to caspase activity. While critical for normal cellular function, anti-anoikis mechanisms become pivotal in cancer cells, fostering their persistence and dissemination to distant organs. In the context of metastasis, the ECM emerges as a key player in tissue formation, growth, and differentiation by delivering essential biochemical and mechanical signals[17]. Additionally, the ECM secretes chemokines, cytokines, and growth factors, creating dynamic microenvironments that regulate cell behavior[18]. Adhesion between cells and interactions with the ECM are vital for the progression of normal epithelial and endothelial cells. However, when these cells detach from their original sites and enter the bloodstream, they become susceptible to metastasis. Understanding the intricate mechanisms of anoikis is paramount in cancer research, offering potential targets for therapeutic interventions aimed at preventing metastasis and enhancing overall treatment efficacy.

3.2. *Streamlining anoikis regulation: unveiling intrinsic and extrinsic pathways*

Anoikis regulation revolves around two primary pathways: the intrinsic (mitochondrial) and extrinsic (death receptor) pathways, elegantly illustrated in Fig. 1. The intrinsic pathway, predominantly governed by the BCL-2 family, intricately manages pro/anti-apoptotic signals, playing a crucial role in programmed cell death[19]. These genes, categorized into anti-apoptotic (*e.g.*, BCL-2, BCL-XL), pro-apoptotic (*e.g.*, BAX, BAK), and "BH3-only" proteins, maintain a delicate balance essential for preventing cancer cell apoptosis evasion[20]. Disruptions in these genes can significantly impact the programmed cell death process.

Within the intrinsic pathway, BH3-only proteins play a pivotal role by initiating the oligomerization of BAX/BAK at the outer mitochondrial membrane. This counters the inhibition by anti-apoptotic proteins, increasing mitochondrial outer membrane permeability and releasing cytochrome c. The released cytochrome *c*, interacting with APAF-1, forms the apoptosome, activating effector caspases and initiating the cascade leading to apoptosis[21]. Mitochondria also release SMAC, a pro-apoptotic factor, which binds to IAPs, relieving their inhibition on caspase-9 and caspase-3, thereby mediating cell apoptosis[22]. The tumor suppressor p53, extensively researched for its role in cancer, can initiate the intrinsic pathway by relieving BCL-2's inhibition on BAX/BAK or activating pro-apoptotic proteins like PUMA through its transcriptional activity, inducing cell apoptosis[23].

In response to external stimuli, the extrinsic pathway involves cell surface death receptors such as FAS, DR4/DR5, TNF-R, and TRAIL-R, binding to specific ligands[24,25]. This initiates death signals activating caspase-8, leading to cell apoptosis through a cascade involving effector caspases[26]. Interconnected with the intrinsic pathway, these mechanisms illustrate the intricate regulation of anoikis, underscoring its significance in the context of cancer development and metastasis.

4. Principles of nanomedicine design for targeting anoikis

Traditional drug treatments often eliminate only those cancer cells susceptible to the treatment, permitting the survival of drug-resistant subgroups like CTCs[27]. CTCs display significant heterogeneity, encompassing variations between epithelial and mesenchymal phenotypes[28]. This hallmark characteristic, indicative of both intertumoral and intratumoral differences, contributes to the survival and clonal expansion of diverse tumor cell subpopulations. Notably, platelets significantly contribute to the metastatic spread of cancer, adding a layer of complexity to tumor heterogeneity[29]. In this context, we explore several key signaling pathways intricately associated with anoikis and discuss therapeutic agents within the realm of nanomedicine designed to counteract anoikis in tumor cells.

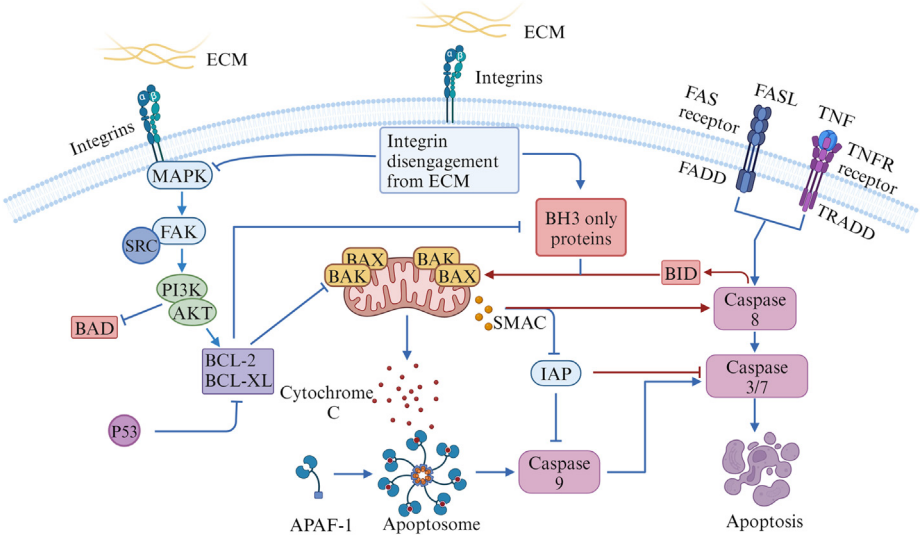

Figure 1 Cell apoptosis pathways upon detachment from ECM. Integrin-mediated signaling initiates two pathways: (1) Intrinsic pathway—integrin signaling activates pathways such as phosphatidylinositol 3-kinase (PI3K) and BCL-2 proteins, triggering the release of cytochrome *c* from mitochondria. This release activates effector caspases, ultimately resulting in apoptosis. (2) Extrinsic pathway—integrin signals activate death receptors (*e.g.*, FAS), which bind to death ligands (*e.g.*, FASL) and form the DISC. Caspase-8 activation through DISC induces effector caspases, leading to cell death. These pathways interact in a coordinated manner, inducing cell apoptosis upon ECM detachment. Created with BioRender.com.

4.1. The integrin-mediated signaling pathways associated with anoikis resistance

When cells detach from the ECM due to prolonged loss of cell−ECM adhesion mediated by integrins, the sentinel process of anoikis is triggered. Integrins, composed of α and β subunits, emerge as primary receptors governing diverse cellular processes, including migration, proliferation, and survival[30]. Their role extends to facilitating cell adhesion to the ECM, a pivotal aspect of cellular functionality[30]. Furthermore, integrins orchestrate bidirectional signaling between the cell and the ECM, transmitting signals that intricately regulate cell survival, proliferation, migration, and differentiation. Upon activation or binding to the ECM, integrins deftly recruit receptor clusters, setting off a chain reaction in intracellular signaling proteins and their downstream effectors.

This intricate dance of signals activates the mitogen-activated protein kinase (MAPK) pathway, thereby triggering focal adhesionkinase (FAK). FAK, in turn, engages with signaling proteins such as phosphoinositide 3-kinase (PI3K)[31] and SRC, a non-receptor membrane-associated protein kinase. This orchestrationactivates FAK, initiating a nuanced interplay of anti/pro-survival signals that effectively inhibit cell apoptosis.

However, disrupting integrin-mediated binding to the ECM precipitates significant consequences. It results in the diminished clustering of receptors, including the epidermal growth factor receptor (EGFR) and peptidyl-tRNA hydrolase 2 (PTRH2; BIT-1; BIT1), on integrins[32]. In response to this disruption, cancer cells strategically upregulate specific integrins, notably $\alpha_v\beta3$[33], to fortify both cell survival and migration. Simultaneously, the activation of the BH3 subfamily of the BCL-2 protein family, encompassing BID and BIM, assumes a pivotal role. These proteins translocate to the mitochondria, orchestrating the release of cytochrome *c* and triggering anoikis—a visually depicted event in Fig. 1.

Despite the threat of anoikis, cancer cells exhibit a remarkable ability to resist. This resistance hinges on the activation of integrin-mediated survival signaling, where key players like FAK and the PI3K/AKT pathway come into play. FAK, a non-receptor tyrosine kinase, takes center stage by phosphorylating downstream targets, including SRC, PI3K, and AKT. This intricate activation sets off pro-survival pathways, finely regulating anti-apoptotic proteins such as BCL-2/BCL-XL. This orchestrated defense mechanism shields the cells against anoikis. Anoikis resistance, a hallmark of tumor cells, is often accompanied by the activation of the survivin pathway, upregulation of matrix metalloproteinases (MMPs), FAK overexpression, and the inactivation of the P53 tumor suppressor[34]. This intricate interplay amplifies metastatic efficiency[34], underscoring the critical importance of unraveling the intricacies of anoikis through integrin-mediated signaling pathways for the development of effective cancer treatment strategies.

4.1.1. Advancements in nanomedicine targeting the PI3K/AKT signaling pathway in cancer therapy

The PI3K/AKT signaling pathway plays a pivotal role in cancer cell survival and critical cellular functions, exhibiting overactivation in various cancers, including gastric, breast, and colon cancer. This overactivation often leads to heightened resistance to apoptosis. The PI3K family of proteins, a group of signaling lipid kinases, phosphorylates phosphoinositides (PIP3) on the cell membrane, triggering AKT activation upon survival factor stimulation. Activated AKT impedes pro-apoptotic proteins, such as BAD, allowing BCL-2 proteins to prevent the oligomerizationof BAX/BAK on the mitochondrial membrane, ultimately suppressing tumor cell apoptosis.

Recognizing the significance of the PI3K/AKT pathway in cancer cells has positioned it as a promising target for drug interventions, resulting in the approval of various inhibitors for cancer therapy (Table 1). Notably, Apatinib has demonstrated efficacy in inducing apoptosis in gastric cancer cells by inhibiting p-PI3K and p-AKT proteins[35]. However, the clinical utility of these inhibitors is hindered by side effects like immunotoxicity, hypertension, rash, and diarrhea[36].

To address these limitations and mitigate systemic toxicity, researchers have explored nanoparticles for targeted drug delivery to cancer cells, enhancing bioavailability and safety while augmenting anti-tumor effects. The combination of PI3K/AKT inhibitors with nanoparticles presents the potential for synergistic inhibition of cancer cell proliferation and improved drug delivery efficiency.

For instance, Au et al.[37] utilized a novel dual Ab pretargeted drug delivery system (PEG-PLGA) to therapeutically deliver BEZ235 to target cells, resulting in reduced drug toxicity and improved antitumor activity. Moreover, research by Patel et al.[38] demonstrated that combining doxorubicin (Dox) with platinum nanoparticles functionalized with polyvinyl pyrrolidone (PVP) enhances the activation of the negative regulatory factor *PTEN*, limiting the PI3K signaling pathway, and achieving anticancer activity against MCF-7 and MDAMB-231 while minimizing drug toxicity. Additionally, Cai et al.[39] developed nanoparticles carrying docetaxel and inhibitor LY294002, enhancing drug accumulation in tumors, ensuring safety and biocompatibility, enabling controlled drug release, and improving anti-tumor activity against gastric cancer.

Researchers are presently investigating nano-drugs that integrate inhibitors of the PI3K/AKT signaling pathway with conventional chemotherapy drugs to address chemotherapy-induced drug resistance effectively. An example of this approach involves the development of a hollow polydopamine nanoparticle loaded with Oxaliplatin, a first-line chemotherapeutic drug, and the dual PI3K/mTOR inhibitor PKI-587 (Gedatolisib). The innovative strategy seeks to counteract the abnormal activation of the PI3K/AKT/mTOR signaling pathway induced by Oxaliplatin, intending to enhance cancer cell apoptosis concurrently and improve overall anti-cancer effects[40].

4.1.2. Unveiling the role of the BCL-2 protein family

4.1.2.1. The protective mechanism against anoikis of the BCL-2 protein family. When cells detach from the ECM, cancer cells undergo abnormal activation of the pro-survival EGFR/*Ras* signaling pathway, fueling their survival and proliferation[41]. RAS, a frequently activated oncogene, interacts with the BCL-2 protein family, facilitating the transmission of signals from cell membrane growth factor receptors to intracellular pathways. This interaction specifically results in the downregulation of the BAK protein, providing a shield against anoikis[42]. Additionally, the PI3K/AKT pathway, intricately linked with apoptosis, exhibits a close association with elements of the BCL-2 protein family[43]. In the realm of cardiac hypertrophy, BCL-2 acts as a downstream component of the PI3K signaling pathway, inhibiting cardiomyocyte apoptosis and fostering cardiac hypertrophy[39,40,44–53].

Various cytokines can trigger members of the BCL-2 protein family, conferring resistance to apoptosis. For instance, kinases

Table 1 Representative clinical trials to target PI3K/AKT signaling pathway and BCL-2 protein family for cancer.

Pathway	Agent	Indication	Status	ClinicalTrials.gov identifier
PI3K	Buparlisib	chronic lymphocytic leukemia	Phase II	NCT02340780
	Taselisib	Advanced lymphoma; advanced malignant solid neoplasm	Phase II	NCT04439175
	PIQRAY (alpelisib)	Advanced or metastatic breast cancer	Approved (2019)	–
	ZYDELIG (Idelalisib)	Relapsed chronic lymphocytic leukemia (CLL)	Approved (2014)	–
AKT	Afuresertib	Breast cancer	Phase I	NCT04851613
	Capivasertib	Advanced lymphoma; advanced malignant solid neoplasm	Phase II	NCT04439123
Dual PI3K/mTOR	Dactolisib	Respiratory tract infections	Phase III	NCT04668352
BCL-2	VENCLEXTA (Venetoclax)	lymphoid and myeloid leukemia	Approved (2016)	–
	G3139	Tumors	Phase I	NCT00543231
	Obatoclax	Acute myeloid leukemia (AML)	Phase II	NCT00684918
BCL-XL	AT-101	Relapsed or refractory B-cell malignancies	Phase II	NCT00275431
BCL-2/BCL-XL/BCL-W	ABT-263	B-cell chronic lymphocytic leukemia	Phase II	NCT00918450

–, not applicable.

JAKs and SRC phosphorylate and activate STAT3, leading to the expression of BCL-XL/BCL-2. TNF-α activates caspase-8 and -10 while simultaneously suppressing apoptosis through NF-κB, resulting in the upregulation of BCL-2. The pro-inflammatory cytokine IL-17A, secreted by activated T cells, assumes a pro-tumorigenic role by modulating MAPK and NF-κB activity. Furthermore, IL-17A promotes tumor angiogenesis by stimulating endothelial fatty acid β-oxidation, enhancing the capacity to resist anoikis, and promoting tumor cell survival[54].

4.1.2.2. Advances in nanomedicine design targeting the BCL-2 protein family. Developing selective BCL-2 inhibitors as a strategy to activate intrinsic apoptotic pathways is an effective approach, aiming to promote tumor cell apoptosis. Certain inhibitors, such as small organic molecules mimicking the BH3 domain, like navitoclax (ABT-263), venetoclax, hypoxoside (Hyp)[55], and sabutoclax, have shown efficacy in cancer patients[56] (Table 1). BH3 domain mimetics exhibit a high affinity for binding to BCL-2/BCL-XL. Notably, venetoclax has been successfully used in treating lymphoid and myeloid leukemia. In acute lung injury treatment, delivering venetoclax using a nanodelivery system based on an amphiphilic polymer improves lung distribution and enhances bioavailability[57].

In breast cancer treatment, an alternative strategy for addressing BCL-2 involves employing the BCL-2-converting peptide NUBCP-9. This distinct inhibitor, unlike others targeting BCL-2, demonstrates anticancer properties by causing a phenotypic shift in BCL-2, transforming it into a pro-apoptotic agent[58]. However, the clinical development of peptide drugs faces challenges such as instability, poor pharmacological properties, low bioavailability, and weak intracellular penetration. Researchers have addressed these issues by developing mesoporous silica nanoparticles coated with folate, loaded with NUBCP-9 peptide, facilitating intracellular peptide delivery for targeted tumor cell treatment[50].

Furthermore, combining paclitaxel (PTX) with NUBCP-9 peptide and incorporating them into PLA-PEG-PPG-PEG nanoparticles as a nanodrug effectively reduces BCL-2 expression, showing strong potential for tumor treatment and avoiding PTX resistance related to BCL-2/BCL-XL upregulation[51]. Recent studies have also demonstrated that small interfering RNA (siRNA) can inhibit pro-survival BCL-2 proteins, inducing cell apoptosis[59]. Various delivery systems like polymer-based nanoparticles and liposomes have been employed to enhance the accumulation of Ginsenoside Rh2 in colorectal cancer cells, thereby reducing BCL-2 expression and increasing caspase expression, ultimately inducing cell apoptosis[60].

In conclusion, employing BCL-2 as a therapeutic target across diverse diseases holds significant promise (Table 2)[39,40,45–53]. Future advancements may revolve around designing and crafting nanodelivery systems housing inhibitors for the BCL-2 protein family alongside anticancer medications. Such systems could heighten drug concentration within target cells, safeguard against degradation, boost bioavailability, optimize pharmacokinetics and distribution, minimize adverse effects, and counter-resistance stemming from BCL-2/BCL-XL upregulation. Furthermore, nanoparticles can be functionalized with targeting ligands to enhance their specificity for cancer cells that overexpress BCL-2. To comprehensively explore the therapeutic capabilities of BCL-2-targeted therapies and enhance their effectiveness and safety profiles, additional research and clinical trials are imperative.

Table 2 Advances of nanomedicine to target PI3K/AKT signaling pathway and BCL-2 protein family.

Nanostructure	Nanoparticle	Target	Indication	Ref.
Polymers	PLGA (TXT + LY294002)	PI3K/AKT	Gastric cancer (GC)	39
Metal nanoparticles	Dox−platinum conjugate system	PI3K/AKT	Breast cancer	45
	MPGNPs + Erlotinib	PI3K/Akt/mTOR	Pancreatic cancer	46
	O/P-HP	PI3K/mTOR	Hepatocellular carcinoma	40
	DPP-SNP/DPP-GNP	P53/BCL-2	Breast cancer	47
	CuO-TiO_2-chitosan-berbamine NPs	P53/BAX	Chronic myelogenous Leukemia (CML)	48
Micelles	NanoGe + NanoCa	PI3K/mTOR	Prognosis of castration-resistant prostate cancer (CRPC)	49
Silica nanoparticles	NUBCP-9-MSNs-FA/NPs	BCL-2	Breast cancer	50
	PTX-NUBCP-9/NPs	BCL-2	Breast cancer	51
Biomimetic nanomedicine	AM@NP(ABT/A12)	MCL-1	Glioblastoma (GBM)	52
Liposomal	Liposomal NPs (miR-214)	P53	Intestinal cancer	53

NanoGe + NanoCa: dual sulfide-crosslinked micelles (DCM) with separate loading of small-molecule inhibitor (Gedatolisib) and chemotherapeutic agent (Cabazitaxel) for targeted drug delivery; O/P-HP: hollow polydopamine-based nanoparticles (H-PDA) loaded with OXA and PKI-587 for nano-delivery system; MPGNPs: macrophage membrane-coated poly(lactic-*co*-glycolic acid) nanoparticles (PLGA NPs) loaded with Gemcitabine; AM@NP(ABT/A12): the biomimetic nanomedicine (AM@NP(ABT/A12)) consists of two key components: an inner core (NP(ABT/A12)) composed of ABT and A12 co-loaded into a pH-sensitive acetal-grafted dextran (a-dextran), and an outer shell comprising a targeting ligand ApoE peptide-functionalized red blood cell membrane (ApoE-RBCm, AM).

4.1.3. Unraveling the P53-dependent apoptotic pathway

4.1.3.1. Navigating anoikis resistance through the P53-related pathway in cancer cells. The transcription factor P53, a pivotal tumor suppressor, springs into action upon encountering various stress signals, such as DNA damage and oncogene expression. When activated, P53 orchestrates a specific set of target genes, putting the brakes on cancer cell growth or initiating apoptosis[61]. Its interaction with BCL-XL/BCL-2 proteins intricately modulates the intrinsic pathway, triggering the release of pro-anoikis effectors BAX/BAK from mitochondria[62]. Expanding its role beyond the intrinsic pathway, P53 stimulates the transcription of the TNFR superfamily pro-anoikis member FAS in the extrinsic pathway[23]. Furthermore, it can induce autophagy by activating autophagy-related gene promoters or initiating death-associated protein kinase (DAPK), contributing significantly to tumor suppression[63].

However, P53, a commonly mutated tumor suppressor gene in cancers, undergoes alterations that not only compromise its tumor-suppressive capabilities but might also confer novel oncogenic properties, fueling tumorigenesis. Dysfunctional P53 emerges as a major contributor to tumor metastasis. For instance, silencing the endogenous P53-R273H contact mutant can reduce AKT phosphorylation, induce the expression of BCL-2 modifying factor (BMF), release BIM from BCL-XL, and sensitize cancer cells to mitochondrial-dependent apoptosis[64]. Additionally, the tumor-suppressing role of wild-type P53 faces negative regulation through proteasomal degradation, orchestrated by the mouse double minute 2 (*Mdm2*) oncogene. The amplification of the *Mdm2* gene in numerous cancer types effectively undermines the functionality of P53 as a tumor suppressor, fostering tumor development[65].

4.1.3.2. P53 gene as a therapeutic target. The *P53* gene stands out as a promising focal point, with the activation of *P53*-related pathways considered a valuable anti-cancer strategy. In clinical trials, inhibiting *MDM2* has demonstrated the ability to activate the *P53* signaling pathway in human tumors. Various effective and selective *P53-MDM2* interaction inhibitors, such as MI-219, MI-319, Nutulin-3, and *MDM2* ubiquitin ligase activity inhibitors, have been discovered[65]. Successful development includes selective mutation Y220C binders that activate the transcriptional activity of mutant *P53*, entering clinical trials[66]. Utilizing nanocarrier systems for drug delivery to activate *P53* is an attractive strategy for cancer treatment (Fig. 2). For glioblastoma multiforme (GBM), researchers developed a tumor-targeting nanocomplex platform efficiently delivering wild-type *P53* plasmid DNA into the nanocomplex platform for delivery to numerous tumor cells and CSCs in primary and metastatic tumors[67]. Another avenue involves the transcription factor P73, belonging to the P53 protein family[68], where the small molecule LEM2, an oxygenated anthraquinone derivative, exhibits TAP73-dependent anti-cancer activity by disrupting protein interactions[69]. Despite being poorly soluble in water, Gomes et al. tackled this issue by developing porous silicon (Psi) nanoparticle (NPs)-based systems, enhancing LEM2 solubility and improving its anti-cancer activity and bioavailability for further *in vivo* investigations[70].

4.2. The characteristics of anti-anoikis are closely related to EMT

4.2.1. Navigating anoikis resistance through EMT signaling

In stark contrast to primary tumor cells, CTCs undergo EMT, endowing them with heightened resistance to immune effector cells, anoikis, chemotherapy, and the mechanical shearing forces induced by blood flow. EMT serves as a pivotal phenotypic state, facilitating metastasis by allowing CTCs to elude anoikis, persist in the circulatory system, and ultimately seed distant organ metastasis[71]. This transition involves three critical phases: (i) the loss of intercellular connections and the epithelial marker E-cadherin, (ii) the acquisition of mesenchymal markers N-cadherin and vimentin, and (iii) profound cytoskeletal alterations to adopt mesenchymal attributes, promoting cell migration, invasion, and resistance to anoikis. The overexpression

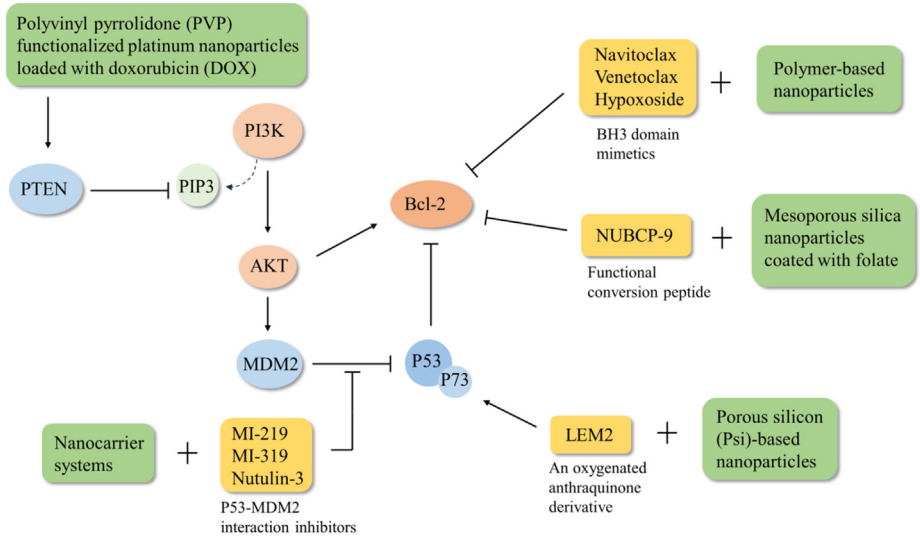

Figure 2 Rational design of nano-agents targeting the PI3K/AKT signaling pathway, BCL-2 protein family, and tumor suppressor P53 based on cell signaling transduction.

of vimentin, a hallmark of EMT in cancer cells, correlates with accelerated tumor growth, invasion, and a poor prognosis[72].

The diminished expression of E-cadherin, a hallmark of EMT, enhances cell mobility, facilitates tumor cell invasion, and reinforces resistance against anoikis. The transcriptional repressor SNAIL, a key E-cadherin regulator (Fig. 3), augments cancer cell metastatic potential during EMT by suppressing epithelial markers and elevating mesenchymal markers[73]. Furthermore, key EMT regulators modulate pro/anti-apoptotic genes, upregulating anti-apoptotic genes (BCL-2 family) and activating pro-survival pathways (*e.g.*, PI3K/AKT) while downregulating pro-apoptotic genes, contributing to anoikis resistance. Interestingly, CTCs exposed to arterial shear stress undergo changes in EMT markers without compromising their anoikis resistance and metastatic ability[74]. EMT induction leads to the upregulation of growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF), activating

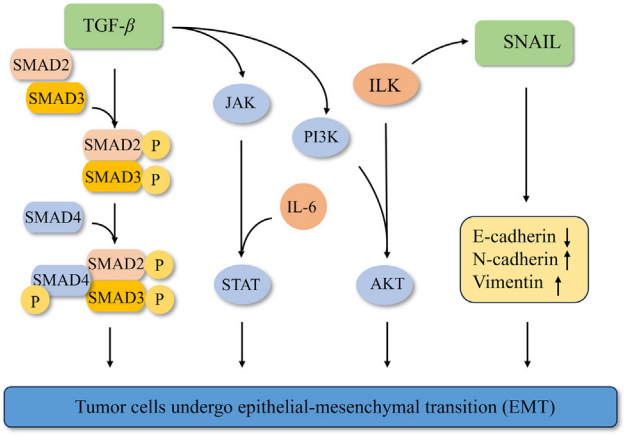

Figure 3 Mechanisms that promote EMT in cancer cells. TGF-β induces EMT through the SMAD signaling pathway. Zinc finger transcription factor SNAIL, the E-cadherin transcriptional repressor, enhances cancer cell metastatic potential during EMT by downregulating epithelial markers and upregulating mesenchymal markers.

survival cascades and fortifying cancer cells' resistance to anoikis[75].

The induction of EMT by TGF-β forms a close association, facilitating anoikis resistance. TGF-β, a pleiotropic regulator, induces EMT through the SMAD signaling pathway. TGF-β1 stimulation leads to the phosphorylation-induced formation of a SMAD2/3 complex, triggering EMT[76]. This activation enables epithelial cells to acquire mesenchymal markers N-cadherin and vimentin[77].

4.2.2. Navigating EMT challenges through nanoparticle innovations

The upregulation of SNAIL not only bestows cancer cells with resistance to anoikis but also instills them with CSC-like characteristics, rendering them resistant to various therapeutic interventions. Previous studies have evidenced that CSCs derived from breast cancer cells exhibit resistance to anoikis induction[78]. Additionally, ILK has been implicated in conferring anoikis resistance in breast cancer cells[79]. Its involvement extends to the regulation of EMT by fostering SNAIL expression, thereby contributing to cancer cell metastasis[80]. The essential roles of ILK and SNAIL make them promising therapeutic targets for impeding metastasis[81].

In response to this challenge, researchers have engineered chitosan nanoparticles (ChNPs) using carboxymethyl dextran (CMD). These nanoparticles were specifically designed to encapsulate SNAIL siRNA alongside the chemotherapeutic agent Dox[82]. Notably, these ChNPs induced significant alterations in the EMT-associated gene expressions. This involved the reduction of MMP-9 and vimentin expression and the elevation of E-cadherin levels in HCT-116 cancer cells. These results highlight the ChNPs' potential to inhibit EMT and counteract metastatic potential. Furthermore, the nanoparticles exerted profound inhibitory effects on cancer cell growth, proliferation, and migration, concurrently inducing apoptotic cell death. Various TGF-β-targeted drugs, including antibodies, small molecules, ligand traps, oligonucleotides, and vaccines, have undergone preclinical and clinical evaluations[83]. Exploring the combination of TGF-β-targeted therapy with conventional treatment modalities is crucial for achieving optimal therapeutic outcomes[84] (Table 3).

Table 3 Representative clinical trials to target EMT for treatment of various diseases.

Target	Agent	Status	Indication	ClinicalTrials.gov
EMT	Simvastatin	Phase II	Breast cancer	NCT03324425
	Abiraterone	–	Prostate cancer	NCT01961843
Vimentin	Pritumumab	Phase I	Malignant primary brain tumors	NCT04396717
	SCMod-1	–	Breast cancer	–
Fibronectin	PYX-201	Phase I	Solid tumor	NCT05720117
	Genotyping	–	Hepatitis B, chronic	NCT06023745
SRC	Dasatinib	Approved (2006)	Lymphoblastic leukemia	
	pyrotinib dimaleate	Approved (2018)	Metastatic breast cancer	
TGF-β	AK-130	Phase I	Advanced malignant tumor	CTR20223096
	GS-18	Phase I/II	Solid tumor	
	Y-101D	Phase I/II	Hepatocellular carcinoma	CTR20230372

–, not applicable.

4.3. *The interplay of autophagy in anoikis resistance*

Autophagy, the intricately regulated self-digestive mechanism housed within lysosomes, emerges as a linchpin in maintaining cellular equilibrium. Its nuanced role in orchestrating the symphony of cancer initiation and metastasis has been unveiled. Activated autophagy in cancer cells conducts a dual performance, fostering cell growth and metastasis, fulfilling energy and nutrient needs, and navigating oxidative stress to pave the way for cancer development. Autophagy takes the lead in safeguarding the activity and physiological functions of CSCs, suppressing cell differentiation, and bestowing upon cancer cells the prowess of boundless proliferation capabilities[85].

4.3.1. *Autophagy's dichotomy in cancer cell development*

Autophagy's role in cancer regulation unfolds as a double-edged sword. In normal cell physiology, it stands as a sentinel against tumors, inhibiting inflammation, eliminating damaged organelles, and reducing cancer cell metastasis. Paradoxically, cancer cells often suppress autophagy to facilitate unhindered proliferation and metastasis. The mTOR protein, a pivotal regulator of cellular autophagy illustrated in Fig. 4, inhibits the initiation of autophagy by phosphorylating ULK1 at Ser75, becoming an accomplice in steering tumor progression[86]. The PI3K/AKT signaling pathway intricately modulates autophagy through mTOR, with the counteracting *PTEN* phosphatase influencing PI3K signaling[87]. Perturbations such as PI3K/AKT overexpression or *PTEN* loss can tip the balance in favor of cancer cell survival. Active nitrogen stress in breast cancer cells activates the ATM damage response pathway, culminating in mTORC1 inhibition, promoting autophagy to prompt cancer cell death[88].

Yet, autophagy unveils its dual nature as a survival strategy for cancer cells facing challenging environments[89]. It acts as a robust survival pathway during ECM detachment and under hypoxia, enhancing cell resilience until reattachment and significantly fortifying resistance to anoikis[90]. Autophagy's adept regulation of cancer cell growth factors, nutrient supply enhancement, stress tolerance improvement, and survival rate elevation underscores its multifaceted role[91]. Crucial proteins like BECLIN 1 participate in protective autophagy, collaborating with CEMIP, a cell migration-inducing protein vital for prostate cancer cells to thwart anoikis[92]. The transcription factor ATF4 in endoplasmic reticulum stress binds to the transcriptional binding site 3 of CEMIP, increasing CEMIP transcription levels. Subsequently, CEMIP facilitates BECLIN1 phosphorylation within prostate cancer cells, impeding the interaction between BECLIN1 and BCL-2. This leads to the heightened dissociation of the BCL-2/BECLIN1 complex, activating the anti-apoptotic BCL-2 and triggering autophagy, ultimately promoting anoikis resistance[93]. ROS, a versatile player, can regulate autophagy, steering cancer development. A certain level of ROS can upregulate the autophagy protein ATG4, inducing protective autophagy and promoting cancer cell growth, migration, and invasion[94]. The delicate balance achieved through autophagy in limiting ROS production *via* the Warburg effect becomes a strategic maneuver for cancer cells, conferring resistance to anoikis and amplifying metastatic capabilities[95].

4.3.2. *Therapeutic frontiers to navigate autophagy*

Charting the course of autophagy regulation emerges as a pivotal therapeutic strategy, particularly in targeting the PI3K–AKT–

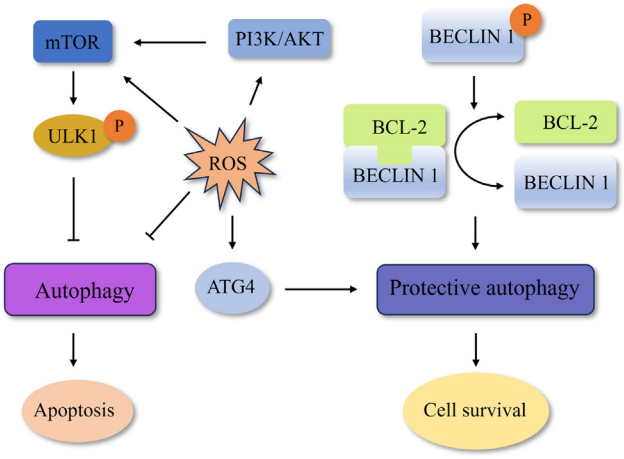

Figure 4 The dual role of autophagy. At the heart of cellular autophagy regulation, mTOR emerges as a central player, steering tumor progression by wielding a dual-edged sword. Its inhibitory prowess targets the initiation phase of autophagy through the phosphorylation of ULK1. The protective alliance between BCL-2 and BECLIN1 is disrupted, unleashing autophagy and fostering cell survival. Moreover, the intricate dance of ROS in the realm of autophagy unfolds a dual role. On one hand, ROS acts as a conductor, inducing protective autophagy by elevating the expression of the autophagic sentinel, ATG4. Simultaneously, ROS directly pulls the strings of autophagy, becoming an accomplice in the intricate orchestration that propels cancer development.

mTOR signaling pathway—a principal orchestrator that stifles autophagy. Inhibiting this pathway becomes a potential catalyst for cancer cell demise through autophagy induction. Deguelin, identified as a potent drug in this arena, introduces a novel therapeutic avenue for pancreatic cancer by triggering autophagy, unveiling new possibilities for treatment[96].

MicroRNAs, the conductors of genetic symphony, play a crucial role in modulating autophagy-related genes. For instance, miR-30a-3p emerges as a maestro in impeding cancer cell migration and invasion by orchestrating the downregulation of ATG12, acting as a guardian against cancer cell metastasis[97]. Furthermore, miR-30a exerts its influence over BECLIN-1, asserting control over autophagy and augmenting cell death attributed to anoikis[98]. Sorafenib, a cornerstone in liver cancer treatment, serves as a maestro shifting the molecular dynamics from protective autophagy to apoptotic autophagy, modulating AKT activity and putting a check on cancer cell development[99].

In the intricate dance of tumor cell metastasis, the evasion of anoikis through triggering protective autophagy takes center stage. The delicate balance of ROS levels upon ECM detachment becomes a linchpin for cancer cells. Strategies targeting ROS to enhance its accumulation in cancer cells present a promising avenue to promote oxidative metabolism, thereby reducing cancer cell resistance to anoikis. Quercetin, showcasing its prowess in inducing apoptosis in breast cancer cells through ROS accumulation, opens new avenues[100]. However, the challenge of quercetin's low oral bioavailability calls for innovative approaches, urging future research to focus on nanocarrier-mediated quercetin co-delivery systems for precision drug delivery[101]. Enterprising solutions, such as the development of a ROS-responsive nanoparticle by Xu et al.[102], underscore the potential to enhance drug delivery to tumor cells effectively. Metal-based nanoparticles, wielding cytotoxicity, induce ROS production, offering a cascade of effects from intracellular oxidative stress to increased cell membrane permeability, culminating in tumor cell apoptosis[103].

4.4. The challenges of anti-anoikis drug targeting delivery and opportunities associated with CTC clustering

Efficiently delivering therapeutic agents to CTCs to induce anoikis, despite extensive studies on the associated signaling pathways, remains a substantial challenge due to their rarity. Technological advancements over the past decade have notably improved CTC detection and analysis, emphasizing their unique characteristics[100]. Nanotechnology has been instrumental in advancing both antigen-dependent and antigen-independent methods. Common approaches involve utilizing CTC antigens, particularly EpCAM, along with CD45-based negative selection for the depletion of hematopoietic cells[104,105]. The $\beta 3$ integrin family, comprising platelet αIIb$\beta 3$ and tumor $\alpha v\beta 3$, interacts with RGD motifs, indicating their crucial role in CTC adhesion and invasion-resisting anoikis in blood flow[106]. RGD-anchored nanoparticles show promise in *in vivo* CTC tracking and preventing cancer metastasis[107]. While leading systems like CellSearch and AdnaTest CTC Select employ immunomagnetic selection, technologies such as magnetic-activated cell separation and geometrically enhanced differential immunocapture diversify capture methods through microfluidics and tailored antibodies[108]. Alternatively, antigen-agnostic methods leverage physical properties for CTC enrichment, with devices like ISET, CTC-iChip, and parsortix detecting CTCs based on size, charge, density, or elasticity, and ongoing developments exploring multimodality approaches for improved sensitivity and specificity. Despite these advancements, implementing innovative *in vivo* CTC detection strategies in clinical settings encounters challenges, including epitope expression variability, cell loss issues, low CTC purity, device-related complexities, blood volume requirements, time constraints, and difficulties in automation[109].

Metastatic colonies' polyclonal nature[110] and the synergistic interactions between subclones[111] underscore the involvement of not solely individual CTCs but also heterogeneous clusters in cancer dissemination[112]. Intratumor hypoxia triggers gene upregulation associated with cell adhesion, facilitating collective CTC cluster shedding[113]. Clustering occurs both homotypically involving interactions among CTCs, and heterotypically encompassing associations with various cell types, *e.g.*, platelets, myeloid cells, and CAFs. These heterotypic clusters, incorporating various cell types and factors, confer advantageous properties promoting viability and metastatic progression[114] (Fig. 5). Recent studies propose disrupting non-tumor cells associated with CTC clusters as a novel therapeutic approach[115]. This approach targets an enlarged population, providing a feasible strategy for delivering anoikis-inducing therapeutic agents to CTCs.

In the swift ballet of circulation, CTCs engage in rapid interactions with platelets, forging a nexus that amplifies plasticity and primes the stage for metastasis initiation[116]. Signal pathways, notably the YAP1 signaling orchestrated by RhoA−MYPT1−PP1, emerge as conductors orchestrating this intricate dance[117]. Furthermore, platelet-derived ATP−P2Y2 interaction masterfully alters vascular permeability, laying the foundation for these dynamic interactions[118]. Amidst this orchestrated interplay, the spotlight turns to platelet-based nanomedicines, unfurling intrinsic advantages in *in vivo* CTC tracking. This revelation not only unravels the mysteries of their interplay but also presents a beacon of hope in the realm of advanced cancer diagnostics and therapeutics, charting a promising avenue in the fight against cancer.

5. Unraveling platelet's anti-anoikis potential in CTCs

5.1. Platelet dynamics in the progression of cancer

The dynamic landscape of cancer investigation reveals an intricate relationship between tumor cells and platelets, a collaboration enhancing cell survival and metastasis[116–118]. Tumor cells orchestrate this alliance, inducing platelet production through thrombopoietin (TPO), a key regulator in IL-6-induced thrombopoiesis[119,120]. As tumor cells transition into CTCs, rapid interactions with platelets lead to activation and aggregation.

CTCs strategically employ survival tactics, initiating tumor cell-induced platelet aggregation (TCIPA)[121], resulting in tumor emboli formation[122]. This shields CTCs from shear forces and aids in evading immune surveillance by NK cells[123](refer to Fig. 5). The molecular components driving TCIPA, including matrix metalloproteinases (MMPs), thromboxane A2 (TXA2), tissue factor (TF), thrombin, and ADP, extend to the initiation of the extrinsic coagulation cascade, activating platelets[124]. In response, platelets undergo dense-granule secretion, a vital signal for cancer-induced aggregation[125].

The tumor microenvironment, rich in IL-6, IL-8, and platelet agonists, catalyzes platelet autophagy and activation, culminating in thrombosis and inadvertently promoting cancer metastasis[126]. Podoplanin expression on cancer cells enhances binding with

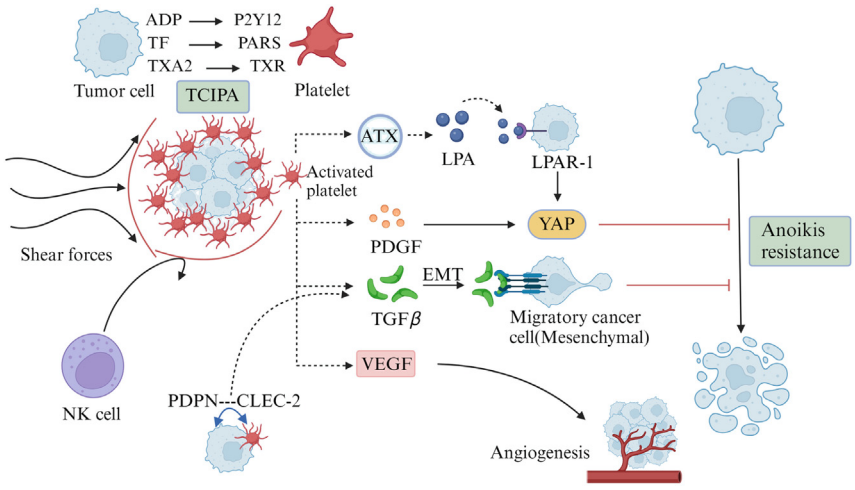

Figure 5 CTC binds to platelets through a variety of molecules, triggering platelet activation and aggregation, a phenomenon known as TCIPA. The formation of TCIPA allows the cancer cells to escape recognition by immune cells, thus promoting CTC survival and metastasis. Activated platelets achieve protection against apoptosis of CTCs by releasing various growth factors for loss of nesting. Created with BioRender.com.

C-type lectin receptor type 2 (CLEC2) on platelets, further promoting aggregation[127]. Notably, certain cancers, like colorectal cancer, activate the BDNF/NF-κB signaling pathway, suppressing anoikis and enhancing metastatic potential[128].

5.2. *The integral role of platelets in cancer progression*

Platelets take center stage as orchestrators in the intricate choreography of tumor metastasis, assuming a central role in cancer dissemination through diverse pathways. Activated platelets, charged with vitality, facilitate cancer spread *via* surface molecules (P-selectin, GPIbα, αIIbβ3) and secreted factors from α-granules (TGF-β, LPA, MMPs) and dense granules (serotonin, ADP, histamine)[7]. Beyond facilitation, platelets release growth factors (TGF-β, PDGF), nurturing tumor growth[129].

Adhesive molecules, including integrins, P-selectin, glycoprotein (GP) Ib-IX-V, and immunoglobulin superfamily members, drive tumor cell adherence during metastatic progression[130]. The interaction between platelet surface molecules and cancer cells underscores their indispensable role in the intricate ballet of cancer dissemination and metastasis. Platelet activation, particularly through P-selectin, leaves an imprint within solid tumors. Activated platelets release angiogenic regulators like VEGF and PDGF, fostering an environment conducive to tumor growth and angiogenesis[131]. Notably, VEGF takes center stage following platelet stimulation *via* the receptor PAR1 triggered by thrombin or TF. Additionally, ADP-induced platelet activation heightens the release of the pro-angiogenic molecule VEGF[132] (Fig. 6).

Platelets play a pivotal role in promoting EMT, enhancing malignant cellular characteristics in cancer cells. Accelerating EMT through the TGF-β signaling pathway[133], platelets mediate aggregation by binding to platelet CLEC2 and inducing TGF-β release. Podoplanin expressed on tumor cells assumes a pivotal role in facilitating EMT and tumor cell extravasation. Recent findings highlight the role of TANK-binding kinase 1 as a mediator, stimulating EMT in breast cells[134]. Furthermore, platelet components such as TSP1 and clusterin regulate MMP-9 through the MAPK pathway, influencing cancer cell invasiveness[135]. This dynamic involvement at multiple stages of tumor metastasis emphasizes platelets' crucial role in tumor progression and dissemination[136].

5.3. *Platelet-induced anoikis resistance in CTC*

Platelet surface-bound P-selectin facilitates platelet adherence to CTCs[137], triggering aggregation and the secretion of autotaxin (ATX). ATX supports CTCs in acquiring resistance to anoikis—a crucial process enabling survival and metastasis[138]. Platelet activation results in the release of Lysophosphatidic acid (LPA), aiding in evading immune responses and fostering invasion and metastasis[139]. Once inside CTCs, LPA binds to LPAR-1, initiating the RhoA—YAP-1 signaling pathway[140]. This activation reinforces CTCs' resistance to anoikis[141,142]. Studies demonstrate that platelets activate YAP1 signaling through the RhoA/MYPT-PP1 pathway, reducing anoikis susceptibility and facilitating metastatic behavior.

PDGF serves as a chemoattractant, stimulating cell proliferation and migration through YAP activation[143]. This activation results in enhanced anoikis resistance and metastasis. Furthermore, PDGF induces YAP dephosphorylation, activating it *via* the RhoA/PP-1 cascade[144]. The interaction between platelets and cancer cells triggers RhoA activation and YAP1 dephosphorylation, facilitated by the PP1-MYPT1 phosphatase. Disrupting this interaction presents an avenue to reduce platelet-induced anoikis resistance[145]. Simultaneous modulation of YAP and PDGF holds promise for enhancing therapy effectiveness. In TNBC, the overexpression of multiple EGF-like domains 11 (MEGF11) boosts tumor cell survival by augmenting anti-anoikis properties, highlighting its role in TNBC cell survival during metastatic dissemination[146].

5.4. *Advances in platelet-associated nanomedicines for cancer therapy*

5.4.1. *Platelet-intrinsic advantages in binding with CTCs and strategy development*

Platelets play a multifaceted role in CTCs, contributing significantly to their evasion of immune recognition and promotion of

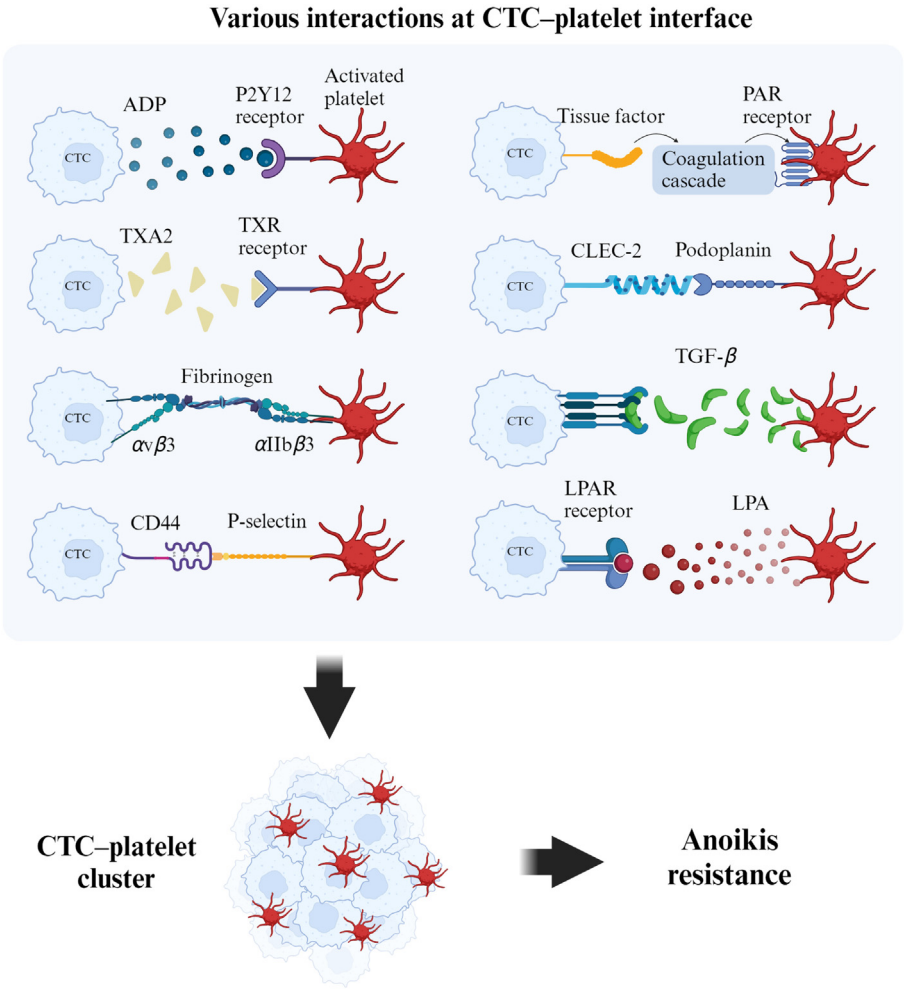

Figure 6 Inherent targeting advantage in platelet−CTC interaction. CTCs initiate platelet activation by employing various factors, including ADP, TXA2, TF, and surface podoplanin. Subsequently, platelets adhere to CTCs through surface adhesion molecules like fibrinogen and P-selectin. Additionally, platelets contribute to the augmentation of anti-apoptotic capabilities in CTCs by secreting cytokines like TGF-β and LPA. Created with BioRender.com.

metastasis. Beyond immune shielding, platelets actively facilitate the EMT by secreting TGF-β. Notably, platelets serve as early pioneers in the formation of the "pre-metastatic niche", orchestrating a microenvironment conducive to tumor cell seeding in the vasculature[147]. Mobilization of granulocytes to CTC−platelet aggregates further enhances this supportive environment for tumor cell seeding. In low-adhesion environments, platelets interact with CTCs, upregulating the expression of GTPase RhoA and activating the YAP1-dependent transcription program. This intricate mechanism induces downstream gene expression related to proliferation and anti-apoptosis, thereby enhancing CTC survival, and promoting metastasis[117]. Additionally, platelets aid in evading NK cell elimination by augmenting the secretion of TGF-β. The secretion of certain substances serves to reduce the expression of the activating immune receptor NKG2D on NK cells, providing additional support to the survival of CTCs[117] (Fig. 6).

The clinical potential of antiplatelet drugs in targeted cancer therapy is substantial, albeit accompanied by concerns about bleeding risks. Addressing these concerns requires innovative technologies. Recent approaches focus on targeting the intricate relationship between platelets and tumor cells, offering promising avenues for future cancer treatments (Table 4). One such strategy involves converting platelets or their membranes into carriers for anticancer agents, exploiting the interactions between cancer cells and platelets. This approach provides several advantages, including extended circulation time, precise targeting, and reduced systemic toxicity. The development of these innovative strategies represents a crucial step toward unlocking the full therapeutic potential of targeting the platelet−CTC relationship in the context of cancer treatment.

5.4.2. Delivery of antiplatelet drugs to inhibit platelet function

Upon entering the bloodstream, tumor cells activate platelets, forming platelet-tumor conjugates that shield tumor cells from mechanical stress and immune surveillance, promoting evasion of anoikis and metastatic dissemination. Nanoparticles can be engineered to deliver platelet inhibitors to tumor tissues, specifically curbing tumor-associated platelet function and thwarting tumor metastasis. As an illustration, liposomal nanoparticles loaded with ticagrelor and integrated with the tumor-homing pentapeptide CREKA (Cys-Arg-Glu-Lys-Ala) exhibit localization to tumor vessel microthrombi, resulting in the inhibition of platelet function[149]. Aspirin, a widely studied antiplatelet medication, not only inhibits COX-1 in platelets but also reduces

Table 4 Advantages of platelets in CTC and discussion of delivery strategies.

Challenge in CTC therapies	Advantage of platelets	Limitation of antiplatelet agent delivery strategies	Advantage of platelet membrane carriers
Complexity and heterogeneity of CTC cluster tumors	Evasion of NK cell-mediated cytotoxicity	Induces thrombocytopenia	Prolonged blood circulation time
Lower drug sensitivity	Early founders of the "pre-metastatic niche"	Elevated risk of bleeding complications	Not easily recognized by the immune system
Intricate interactions between CTCs and immune cells	Enhances anoikis resistance of CTCs	Side effects of antiplatelet medications	Significantly more efficient targeting of cancer cells
Precise targeting of CTCs	Innate immune cells and exhibit some anticancer properties[148]	Translating in a clinical setting is very difficult	Minimizing medication side effects

the production of PGE2 and TXA2, attenuating tumor metastasis and improving survival rates in breast cancer and endometrial cancer[150−152]. Nevertheless, certain clinical investigations have suggested that aspirin does not influence cancer risk or cancer-specific mortality[153,154]. More clinical trials are crucial to substantiate both aspirin's preventive and therapeutic effects in cancer treatment.

Inhibiting platelet function can also be achieved by blocking the release of growth factors from platelets *via* antibodies or small molecules (*e.g.*, PDGF, TGF, VEGF). For example, inhibiting TGF secretion by platelets prevents tumor cells from undergoing EMT, hindering tumor cell growth and metastasis. Platelet blockade, by curtailing TGF-β production at its source, could enhance immunity and augment cancer therapy[155]. Researchers have designed biocompatible nanoparticles, such as PTX@AlbSNO, to release NO and PTX, blocking platelet-tumor cell interactions and inhibiting TGF-β secretion, potentially enhancing cancer therapy[155]. Notably, platelet depletion enhances tumor vasculature permeability, facilitating improved penetration of anticancer agents into tumors[156,157]. Innovative nanocarrier systems have been developed to co-deliver antiplatelet agents and chemotherapeutic drugs, capitalizing on this phenomenon. For instance, polymer-lipid-peptide (PLP) nanoparticles were employed to deliver the platelet-inhibiting antibody R300 and the anti-cancer drugDox[158]. PLP selectively released R300 in the vicinity of tumor-associated platelets, locally depleting the tumor and enhancing drug accumulation.

5.4.3. *Delivery of antiplatelet drugs to target tumor-based platelets by nanoparticles*

While the use of antiplatelet medications may cause thrombocytopenia and bleeding complications[159], research has shown that prolonged platelet function suppression could lead to adverse outcomes. For example, the administration of dual antiplatelet inhibitors, clopidogrel, and aspirin, to mice with 4T1 metastatic breast cancer resulted in decreased survival rates[160]. The emergence of novel antiplatelet agents with improved safety profiles underscores the necessity to mitigate the side effects of antiplatelet drugs, thereby fully exploring their clinical potential.

However, systemic administration of anti-platelet drugs often results in the impairment of autologous platelets and disruption of their functions, particularly in coagulation processes. To address this concern, nanoparticles integrated with targeted delivery capabilities provide a potential solution. By evading harm to the body's own platelets, they enable precise administration directly at the tumor site, thereby augmenting the efficacy. In the initial stages, researchers adapted nanoparticles by incorporating tumor-targeting ligands like the CREKA peptide[149], TM33 peptide[161], fucoidan segment[162], and P-selectin-targeting peptide[163]. These ligands were coupled with platelet inhibitors, aiming to concentrate the treatment in close proximity to tumor cells (Table 5)[149,164−170].

5.4.4. *Application of platelet membranes as biological carriers in targeting CTCs*

The impetus for developing platelet-based nanoparticles, such as platelet-based drug delivery systems and platelet membrane-

Table 5 Advances in nanoparticles for delivery of antiplatelet drugs.

Nanoparticle	Nanoplatform	Drug	Application	Ref.
PTX@AlbSNO	*S*-Nitroso albumin	PTX/NO	Reverses tumor immunosuppression	164
TM33-GON/TNA	TM33 peptide-modified Gelatin/oleic acid NPs	Tanshinone IIA (TNA)	Pancreatic cancer	165
cRGD-liposomes	Liposomal nanoparticles	RGD peptide	Targeting specificity to tumor	166
PCLP-CUR	Liposomes modified with chitosan	Curcumin	Cancer therapy	167
FD/DOX	Fucoidan-functionalized micelle	DOX	Reverses tumor immunosuppression	168
PFTBA@Alb	Albumin-modified NPs	Perfluorotributylamine (PFTBA)	Immunotherapy	169
CREKA-Lipo-T	Liposomal NPs bearing the CREKA	Ticagrelor	Blocks tumor metastasis	149
PLP-D-R	Polymer-lipid-peptide NPs	Doxorubicin/antiplatelet antibody R300	Cancer therapy	170

encapsulated nanoparticles, stems from the active targeting of cancer cells by platelets (Table 6)[171–187].

Platelet membranes, functioning as efficient drug delivery carriers, maintain essential platelet traits like surface molecules and proteins. This characteristic aids in reducing immunogenicity and facilitates precise targeting of cancer cells[188]. In cancer, the overexpression of P-Selectin receptors on platelet membranes aligns with excessive CD44 receptors on cancer cell surfaces, enabling active targeting and precise delivery of anticancer drugs[189]. Hu's group[190] developed TRAIL-Dox-PM-NV, encapsulating anticancer protein-TRAIL and cytotoxic agent-Dox, achieving synergistic anti-tumor efficacy and eliminating

Table 6 The primary applications of platelets and platelet membrane as biological nanovehicle.

Vehicle	Nanoparticle	Drug	Disease type	Cell line	Ref.
Platelets	DOX-platelet	DOX	Lymphoma	Raji	171
	Plt@ND-DOX	DOX	Malignant tumor	LLC	172
	DOX-platelet-CD22	DOX/anti-CD22 monoclonal antibodies (mAb)	Lymphoma	Raji/Mino	173
Platelet Membrane (PLTM)	RAP@PLT NPs	RAP	Atherosclerosis	RAW264.7	174
	PLT-PPy-DOX	Dox/PPy	Hepatocellular carcinoma (HCC)	HCC	175
	PNP-R848	Resiquimod (R848)	Solid tumor	MC38	176
	PM-W18O49-Met NPs	Metformin	Alleviate tumor hypoxia	Raji	177
	(SFN + TPL)@CPLCNPs	Sorafenib/Triptolide	HCC	Huh-7/RAW 264.7	178
	Hb-LOX-DOX-ZIF8@PM NPs	Hb/LOX/DOX	Cancer therapy	HUVECs/4T1	179
	cRGD-platelet @MnO/MSN@PPARα/LXRα	PPARα/LXRα	Atherosclerosis	THP-1	180
	PMVs@PLGA-miRNA	microRNA inhibitors	Myocardial ischemia −reperfusion injury	H9C2/HEK-293T	181
	DOX-PEVs	DOX	Breast cancer	MDA-MB-231	182
Hybrid Membrane	DLMSN@Dox/IR780 NPs	DOX/IR780	Triple negative breast cancer	4T1	183
	Au-Hb@PLT	Au/Hb	Alleviate tumor hypoxia	HeLa/HEK	184
	PLT@BPQDs-HED	Hederagenin	Cancer therapy	MCF-7	185
	PH-HCM@FeCNDs	–	Breast cancer	4T1	186
	PCNPs	β-Mangostin	Glioma	THP-1	187

–, not applicable.

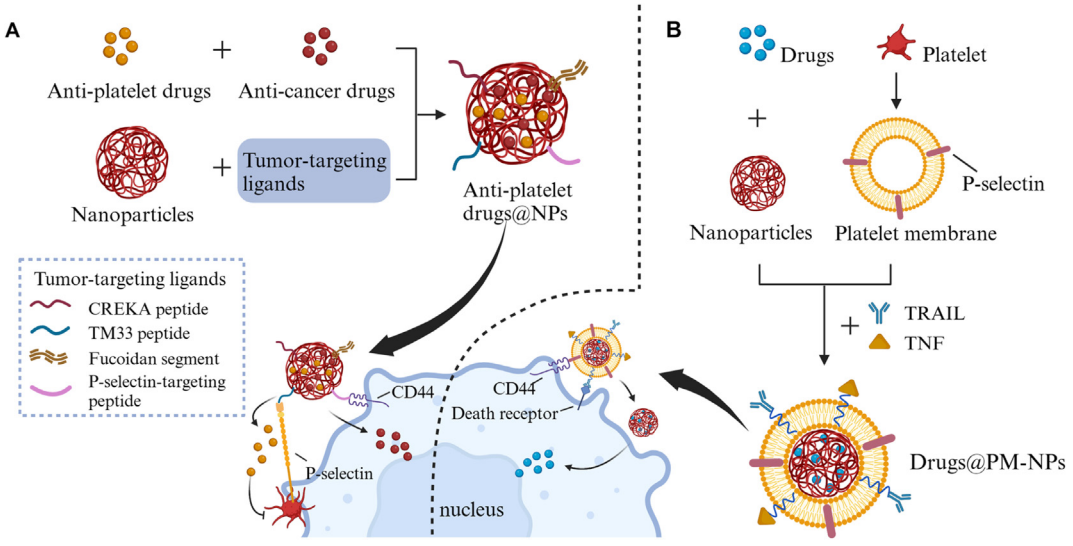

Figure 7 Strategies for the development of platelet-based nanoparticles involve (A) the incorporation of antiplatelet drugs and chemotherapeutic agents into the nanoparticles, along with the modification of tumor-targeting ligands to facilitate drug delivery to the tumor site. In this context, the nanoparticles are designed to utilize the recognition of coagulated plasma proteins by the CREKA peptide to selectively target tumors, and the specific binding of activated platelets' P-selectin by the TM33 peptide. This approach aims to boost drug delivery efficacy to the intended tumor site. Additionally, (B) the schematic design of platelet membrane-based nanoparticles is integral to this strategy. Created with BioRender.com.

metastatic tumor cells. Additionally, Hu's team[191] designed platelet membrane-coated polymer nanoparticles delivering chemotherapeutic agents CTCs. Modified with platelet membranes, these carriers significantly enhance targeting capabilities[192] (Fig. 7).

In a study, researchers devised a therapy approach for lymphoma employing platelets loaded with Dox[193]. The findings demonstrated the efficacy of the Dox−platelet combination in delivering the payload to the desired site, showcasing the potential of platelets as effective carriers for clinical lymphoma therapy. However, it's crucial to note that the *in vitro* preparation of platelet carriers poses challenges due to processes like centrifugation, washing, agitation, and temperature fluctuations, which can trigger platelet activation and thrombus formation. Consequently, *in vitro* platelet preparation remains intricate, resulting in low yield and limited storage time[194−196].

Functionalized silica nanoparticles coated with platelet membranes offer a promising avenue, particularly in inhibiting the abnormal spread of breast cancer cells[197]. King's group devised an innovative approach to modify TRAIL on platelet membrane-coated SiO_2 nanoparticles. In an animal model of lung metastasis, this nanoplatform demonstrated potent antimetastatic effects, significantly reducing tumor nodule formation in the lungs[198]. Another study utilized mesoporous silica nanoparticles to coat drugs with platelet membranes, incorporating vascular disruption agents. This strategy effectively disrupted tumor vasculature and exhibited strong antiangiogenic effectiveness. The platelet membrane facilitated targeted adhesion at damaged vessel walls within the tumor, enhancing the therapeutic impact[199].

Platelet membrane-based drug delivery systems hold promise in cancer treatment. Leveraging platelet functional properties in combination with nanotechnology offers potential in CTC research. Notably, nanoparticles incorporating apoptosis-associated agents (*e.g.*, TRAIL, TNF, FAS ligand) and liposomes encapsulating siRNA exhibit potential in extending the overall survival of cancer patients[200]. Additionally, antiplatelet therapy in cancer could be a potent tool when combined with other cancer treatment strategies.

6. Conclusions and outlooks

In conclusion, the intricate landscape of CTCs, particularly their ability to resist anoikis and their complex interactions with platelets, underscores the critical role these phenomena play in tumor metastasis. A comprehensive understanding of the molecular pathways governing anoikis resistance not only fuels academic inquiry but also holds significant therapeutic promise. This will facilitate the discovery of more potent and precisely targeted treatment modalities. Concurrently, the field of nanomedicine emerges as a transformative force in cancer treatment, offering attributes such as precise targeting, expansive drug loading capacity, reduced toxicity, and heightened bioavailability. Future research endeavors must prioritize enhanced precision and stability to unlock the full potential of nanocarriers in addressing the challenges of tumor growth and metastasis.

Moreover, CTCs, characterized by their rarity and heterogeneous morphology and phenotype, present formidable challenges in identification and isolation. Leveraging platelet-cancer cell interactions for effective CTC and tumor targeting holds promise for future cancer treatments. However, three key challenges must be addressed to advance this approach. Firstly, storage and preservation of platelet systems for extended periods require careful consideration, especially regarding potential changes induced by lyophilization and cold storage[194−196]. Second, maintaining the circulation time of altered platelets, essential for effective drug delivery, necessitates a deeper understanding of clearance mechanisms[195,201,202]. Lastly, optimizing loading methods, drawing inspiration from parallel techniques, holds the key to enhancing platelet-based nanomedicines aimed at treating primary tumors and CTCs[184,203,204].

The first challenge involves addressing the storage and preservation of platelets, crucial for effective platelet-based drug delivery. While most studies use freshly prepared platelet formulations, practical clinical applications demand readily available formulations of loaded platelets. Overcoming challenges related to lyophilization and cold storage is imperative, considering potential changes in platelet pharmacokinetics. Additionally, glycosylation and receptor inhibition methods require further exploration for compatibility with platelet-based carriers[195,196]. The second challenge centers on preserving the circulation time of platelets, which significantly decreases with altered storage conditions[195,202]. New methodologies are needed to prolong carrier circulation by comprehending clearance mechanisms and optimizing platelet conditions for prolonged circulation. The third challenge involves optimizing loading methods to enhance the efficiency and effectiveness of platelet-based drug delivery systems. Techniques such as lipid nanoparticles[203], superparamagnetic nanoparticles[204], and sonoporation[184] show promise in achieving high-yield loading with minimal morphological changes to platelet carriers. Refinement of these loading techniques holds the potential to create more potent nanosystems specifically designed for eradicating both primary tumors and CTCs, utilizing platelets as a crucial component.

As we contemplate the future, the anoikis-platelet interface emerges as a frontier with immense potential for targeted therapy against CTCs. Advances in research and technology offer the prospect of engineering nanoparticles tailored for the selective targeting and elimination of CTCs, promising innovative strategies in the battle against tumor metastasis and fostering hope for improved therapeutic outcomes and elevated survival rates among cancer patients.

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Author contributions

Manqing Tang, Zhijie Zhang and Ping Wang conceived and wrote the manuscript, drew the figures. Feng Zhao organized the tables. Lin Miao and Yuming Wang supervised the project. Yingpeng Li, Yunfei Li and Zhonggao Gao conceptualized the article, supervision, and revised the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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