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Emerging role of exosomes in cancer therapy: progress and challenges

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Abstract

This review highlights recent progress in exosome-based drug delivery for cancer therapy, covering exosome biogenesis, cargo selection mechanisms, and their application across multiple cancer types. As small extracellular vesicles, exosomes exhibit high biocompatibility and low immunogenicity, making them ideal drug delivery vehicles capable of efficiently targeting cancer cells, minimizing off-target damage and side effects. This review aims to explore the potential of exosomes in cancer therapy, with a focus on applications in chemotherapy, gene therapy, and immunomodulation. Additionally, challenges related to exosome production and standardization are analyzed, highlighting the importance of addressing these issues for their clinical application. In conclusion, exosome-based drug delivery systems offer promising potential for future cancer therapies. Further research should aim to enhance production efficiency and facilitate clinical translation, paving the way for innovative cancer treatment strategies.

Keywords Exosomes, Exosome-based drug delivery, Cancer therapy, Clinical application

Introduction

Background on exosome-based drug delivery

Exosomes, small extracellular vesicles released by most cell types, have attracted growing interest for their key role in cell communication and potential as therapeutic carriers. These vesicles, usually 30 to 150 nanometers in size, originate from the endosomal pathway and have a lipid bilayer containing biomolecules like proteins, lipids, and nucleic acids (Fig. 1). Their biocompatibility, capacity to cross biological barriers, and low immunogenicity make them highly suitable for drug delivery, particularly in cancer therapy [1]. Exosome-mediated drug delivery is emerging as a promising strategy due to their natural ability to target particular cells, aided by surface proteins and ligands that identify and attach to target cells [2]. Moreover, exosomes can carry various therapeutic agents, such as small molecules, nucleic acids, and proteins, to recipient cells, improving the precision of cancer treatments [3].

Recent progress in nanotechnology has led to the development of engineered exosomes aimed at optimizing drug delivery efficiency. For example, exosomes can carry chemotherapeutic drugs or genetic material to selectively target cancer cells while reducing systemic toxicity [4]. The small size and capacity to fuse with cellular membranes enable efficient drug delivery across physiological barriers like the blood-brain barrier, a major obstacle in treating brain cancers. These characteristics make exosomes a strongly hopeful drug transport system for targeted cancer therapies, capable of overcoming many limitations of conventional methods [5].

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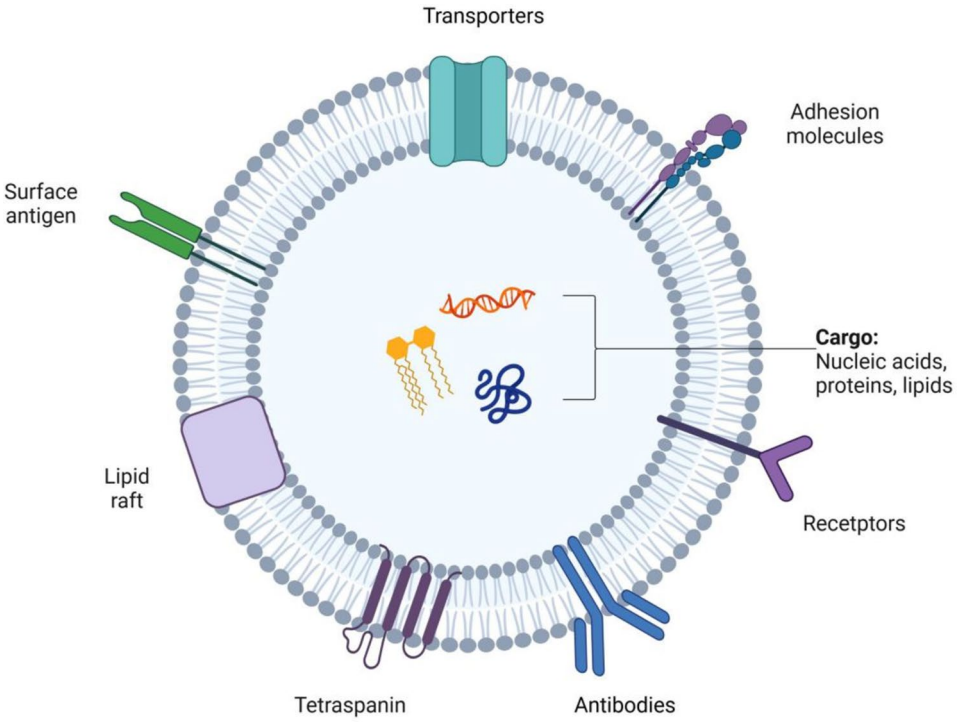

Fig. 1 A representative scheme of exosomal composition. Exosomes encompass cellular lipids, proteins, and nucleic acids, mirroring the state and function of their parent cell. Comprehending their formation is crucial for exploiting EVs in diagnostic and therapeutic applications

Importance of exosome-based drug delivery

The significance of exosome-mediated drug delivery for cancer treatment is highlighted by its numerous advantages over traditional systems. One of the most significant benefits is the high biocompatibility and low immunogenicity of exosomes, which originate from the body's own cells. This minimizes the risk of immune reactions, making them an ideal carrier for delivering treatments to cancer patients, who often have weakened immune systems [6]. In addition, exosomes have an innate ability to home in on specific tissues, particularly tumors, through receptor-ligand interactions, enhancing the precision of drug targeting. Targeted delivery limits healthy tissue exposure to toxic drugs, reducing side effects and enhancing the therapeutic index of cancer treatments.Furthermore, exosomes can be modified to carry a variety of medicinal payloads, including chemotherapeutic drugs, small interfering RNA (siRNA), and microRNA (miRNA), which allows for versatile applications in treating different types of cancer. Their ability to protect these cargoes from degradation in the bloodstream also enhances the stability and bioavailability of the delivered therapeutics, further increasing the efficacy of cancer treatments [7]. These unique properties of exosomes position them as a transformative technology in the field of oncology, with the potential to improve patient outcomes in various cancers, including those that are traditionally difficult to treat, such as brain and pancreatic cancer [8].

Tumor-derived exosomes, despite their advantages, can also promote tumor growth, metastasis, and angiogenesis through multiple mechanisms [9]. They carry oncogenic proteins and RNAs that can alter recipient cell phenotypes, degrade the extracellular matrix to facilitate invasion, establish pre-metastatic niches in distant tissues, and enhance angiogenesis via pro-angiogenic factors. Furthermore, they can suppress host immune responses, helping tumor cells evade immune surveillance [10]. These tumor-promoting properties pose significant safety concerns when considering tumor-derived exosomes as drug delivery systems (DDS). To address these concerns, selecting an appropriate cell source for exosome production is crucial. Non-tumorigenic cells, such as mesenchymal stem cells (MSCs) or immune cells, provide a potentially safer alternative for therapeutic applications due to their modifiability, which can enhance therapeutic efficacy while minimizing adverse effects [11].Advancing exosome-based therapies also requires careful screening and modification of exosome content to mitigate risks. Techniques such as genetic engineering or loading exosomes with therapeutic agents to counteract tumor-promoting factors can maximize therapeutic benefits while minimizing risks [12]. The next steps for developing exosome-based DDS include standardizing isolation methods, thorough characterization, and ensuring safety in preclinical and clinical trials. Engineered exosomes, capable of targeted drug delivery and improved safety,

represent a transformative technology in oncology, paving the way for more effective and personalized cancer treatments [13].

While the latest few reviews summarize the recent advancements in exosome research, they also highlight the bottlenecks and challenges in large-scale production, optimizing loading efficiency, and ensuring stability. However, the latest few reviews not systematically review the progress made in cancer treatment, nor do they clarify how exosome-based therapies could pave the way for future personalized medicine. Furthermore, they do not provide an in-depth analysis of the challenges that exosomes still face in cancer therapy, or the measures required to overcome them [14, 15].This review offers a thorough overview of recent progress in exosome-mediated drug delivery for cancer therapy. It begins with a discussion of the mechanisms of exosome formation and cargo loading, highlighting the biogenesis of exosomes and the strategies employed to incorporate therapeutic agents into these nanovesicles. The advantages of using exosomes, such as their high biocompatibility, targeted delivery capabilities, and improved drug stability, are examined in detail. Furthermore, the review explores the latest innovations in exosome engineering, including surface modification techniques, novel cargo-loading methods, and the development of hybrid exosome-nanoparticle systems. In addition to covering the applications of exosome- mediated drug delivery in chemotherapy, gene therapy, and immunotherapy, this review also addresses the challenges and limitations of exosome manufacturing, scalability, and clinical translation. Finally, the review concludes with an exploration of emerging trends and potential solutions to overcome the current obstacles in the field, offering insights into the future directions of exosome-based cancer therapies.

Mechanisms of exosome formation and cargo loading

Biogenesis of exosomes

Exosomes are small extracellular vesicles (EVs) that originate from the endosomal system. Their biogenesis involves multiple steps, starting with early endosome formation through plasma membrane folding, followed by maturation into multivesicular bodies (MVBs). During this process, inward folding of the MVB membrane forms intraluminal vesicles (ILVs), which become exosomes when MVBs merge with the plasma membrane and release them into the extracellular space [16] (Fig. 2). Exosome biogenesis is regulated by the endosomal sorting complexes required for transport (ESCRT) machinery, which is crucial for sorting cargo molecules, such as proteins, nucleic acids, and lipids, into ILVs [17]. In addition to ESCRT, other molecular components such as Rab GTPases, tetraspanins (e.g., CD63, CD81), and Alix also contribute to the regulation of exosome formation, ensuring the specificity of cargo selection and vesicle formation [18] (Fig. 3).

The release of exosomes is tightly controlled by cellular signaling pathways and varies depending on the physiological state of the cell. For instance, in cancer, exosome biogenesis can be upregulated, leading to increased secretion of tumor-derived exosomes that carry oncogenic factors, which can promote tumor growth, metastasis, and immune evasion. Exosome biogenesis and secretion are thus seen as potential therapeutic targets, as modulating these processes could disrupt pathological interactions between tumor cells and their microenvironment. Exosome biogenesis is a highly dynamic and intricate process, with multiple regulatory checkpoints that ensure the precise loading and release of bioactive cargo [19].

Cargo selection and loading mechanisms

The process of selecting and loading cargo into exosomes is highly specific and involves both passive and active mechanisms. Cargo molecules such as proteins, lipids, and various types of RNA (including mRNA, miRNA, and lncRNA) are selectively incorporated into exosomes through molecular sorting pathways that are modulated by specific proteins. The ESCRT machinery plays a central role in sorting ubiquitinated proteins into exosomes, while proteins like Alix and TSG101 assist in cargo selection by interacting with these molecules and directing them into ILVs [20]. Tetraspanins, such as CD9, CD63, and CD81, also facilitate the packaging of specific cargo molecules, contributing to the functional diversity of exosomes [21].

In addition to proteins, nucleic acids are selectively loaded into exosomes. RNA-binding proteins such as hnRNPA2B1 recognize specific RNA sequences and mediate their incorporation into exosomes. This selective RNA sorting enables exosomes to carry regulatory molecules that affect gene activity in recipient cells, contributing to processes like tumor growth and immune response [22]. The lipid composition of exosomes also influences cargo selection, as lipid rafts enriched in cholesterol and sphingolipids can aid in the recruitment of specific proteins and other molecules into exosomes [23].

Recent advancements in exosome engineering have enabled researchers to manipulate the cargo loading process for therapeutic purposes. Both passive and active loading strategies are used to incorporate drugs, nucleic acids, and other therapeutic agents into exosomes. Passive loading relies on the natural uptake of small molecules by exosomes during their biogenesis, while active loading techniques such as electroporation and chemical modifications enhance the encapsulation efficiency of larger or charged molecules. These engineered exosomes

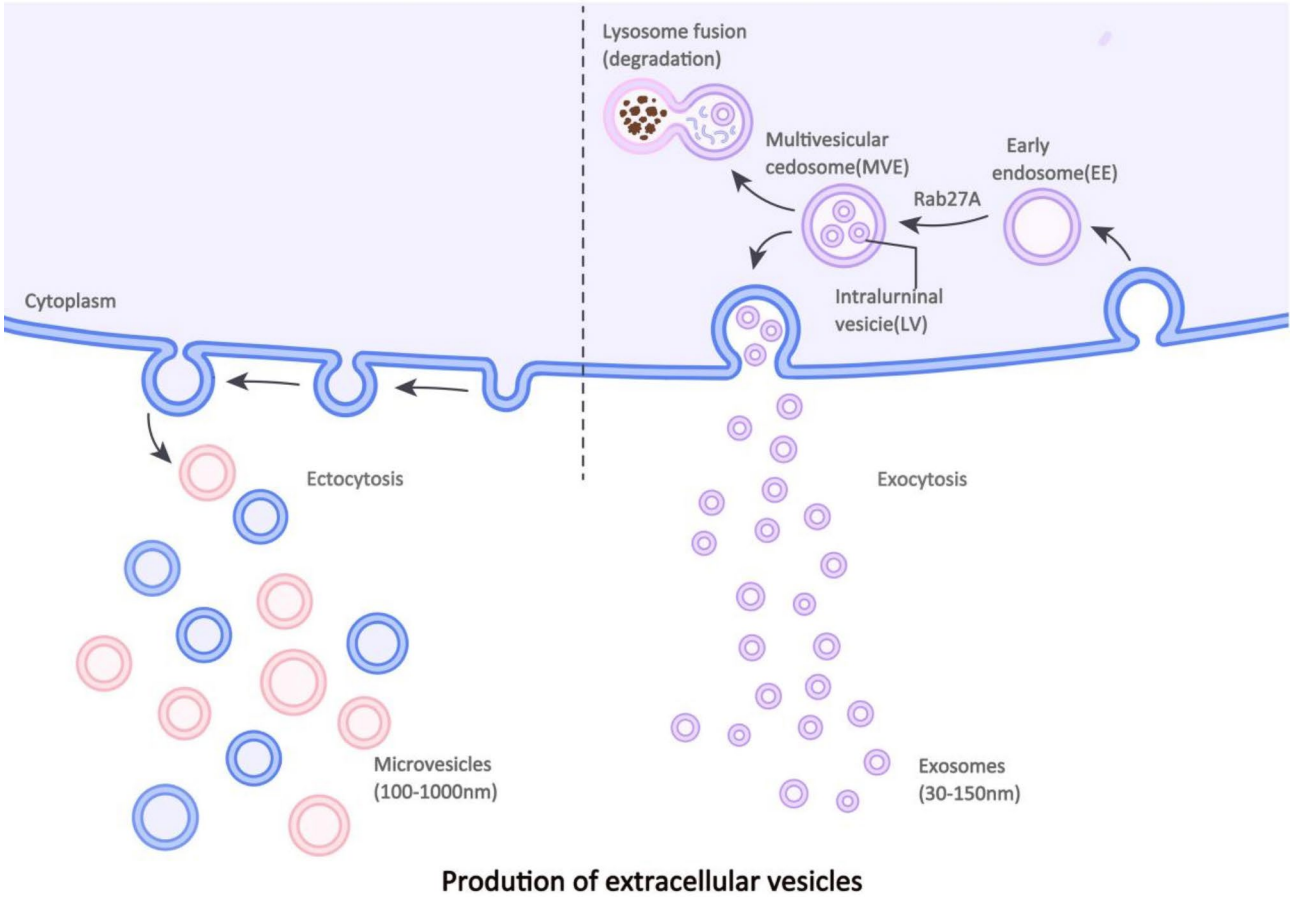

Fig. 2 Production of extracellular vesicles. The formation of extracellular vesicles. EVs are membrane-enclosed particles discharged by cells and categorized into exosomes, microvesicles, and apoptotic bodies in accordance with their origin and size. Exosomes are formed within multivesicular bodies and are released when these bodies merge with the plasma membrane. Microvesicles sprout directly from the plasma membrane, while apoptotic bodies arise from cell fragmentation during apoptosis

have demonstrated strong potential as drug carriers, providing targeted delivery, reduced toxicity, and improved therapeutic effectiveness in preclinical models. Understanding the mechanisms of cargo selection and loading is essential for advancing exosome use in disease treatment, especially for cancer and neurodegenerative conditions [24, 25].

Advantages of exosome-based drug delivery systems

High biocompatibility and low immunogenicity

A key advantage of exosome-mediated drug delivery is their high biocompatibility and low immunogenicity. As exosomes are naturally occurring vesicles from the body's cells, they minimize immune response risks. Unlike synthetic nanocarriers such as liposomes or polymer-based systems, exosomes are less likely to trigger adverse reactions, making them a safer option for therapeutic applications [26]. This natural origin allows exosomes to circulate in the body for extended periods, enhancing their capacity to deliver treatments effectively while reducing the risk of immune clearance.

Exosome-based drug delivery systems also exhibit excellent biodegradability and low toxicity, which are critical for avoiding accumulation within the body. For example, exosomes used in bone-targeting therapies have shown promising results in preventing bone loss and promoting bone formation without causing significant immune responses [27]. Additionally, cancer cell-derived exosomes have been studied for their capacity to deliver drugs specifically to tumors, leveraging their low toxicity and immunogenicity to improve precision medicine approaches. This biocompatibility feature is key to their potential use in delivering therapeutic agents across different physiological barriers, such as the blood-brain barrier, which is often challenging for conventional drug delivery systems [6].

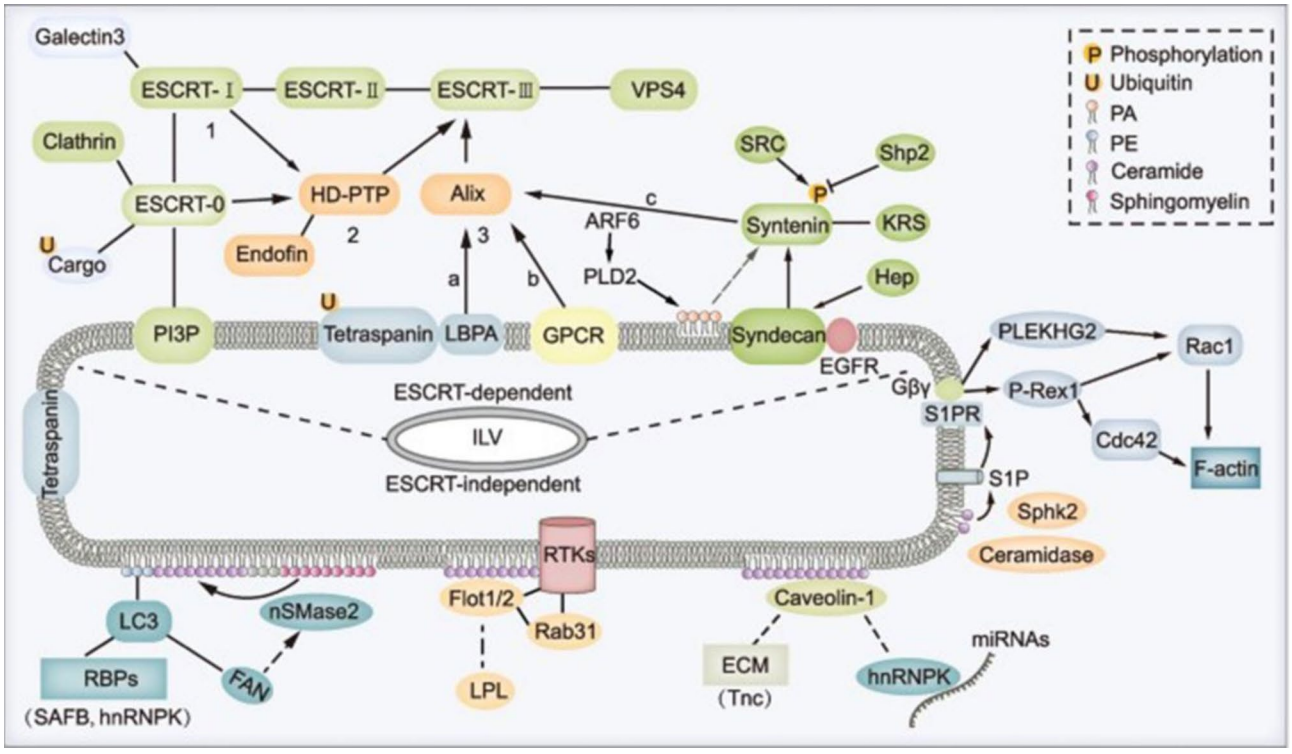

Fig. 3 Multiple mechanisms regulate the formation of ILVs. Reproduced from ref. 17 with permission from Springer Nature copyright 2022

Enhanced targeting capabilities and drug stability

Another significant advantage of exosome-based drug delivery systems is their enhanced targeting capabilities and ability to improve drug stability. Exosomes naturally contain surface proteins and ligands that enable them to recognize and bind to specific cells or tissues, thus ensuring precise delivery of therapeutic agents [28]. This targeting ability can be further enhanced through bioengineering techniques, where specific ligands or receptors are incorporated into the exosome membrane to improve its affinity for certain tumor cells or disease sites [29]. This allows exosome-based therapies to concentrate drugs at the desired site while minimizing off-target effects, which is particularly important in cancer treatment, where high drug specificity can significantly reduce toxicity to healthy tissues [30].

In addition to targeting capabilities, exosomes enhance drug stability by protecting therapeutic agents from degradation in the bloodstream. The encapsulation of drugs within the lipid bilayer of exosomes shields them from enzymatic degradation and harsh biological environments, increasing their bioavailability and effectiveness. This feature has been particularly beneficial for the delivery of nucleic acid-based therapies, such as mRNA or siRNA, which are highly susceptible to degradation. By using exosomes as carriers, these molecules can be delivered intact to the target cells, where they can exert their therapeutic effects more efficiently. Exosomes' natural ability to ensure drug stability, combined with their targeting capabilities, makes them an attractive platform for next-generation drug delivery systems [31].

The dual functions of exosomes

Exosomes are natural nanocarriers that inherit the molecular characteristics of their donor cells, including proteins, lipids, and nucleic acids, which can significantly influence their therapeutic potential in gene therapy and immunotherapy [32]. This cargo can exert either synergistic or antagonistic effects on therapeutic outcomes. For instance, exosomes derived from immune cells such as dendritic cells may enhance immune responses by carrying MHC molecules and co-stimulatory signals, thereby boosting T-cell activation and promoting anti-tumor immunity [33]. On the other hand, exosomes originating from tumor cells may carry immunosuppressive molecules like PD-L1, which can inhibit T-cell function and promote immune evasion, counteracting the goals of immunotherapy [34]. Thus, while exosomes offer great promise as drug delivery systems, careful consideration of their endogenous cargo is necessary. Strategies like engineering exosomes to modify or replace detrimental components can mitigate negative effects, enhance targeting capabilities, and ultimately improve the efficacy of exosome-based therapies.

Exosome delivery strategies

Natural exosomes

Natural exosomes are extracellular vesicles produced by various cell types, naturally released into the extracellular environment. They are collected from biological fluids (e.g., blood, urine, saliva) or cell culture supernatants [35]. Natural exosomes have gained significant attention as efficient drug delivery vehicles. Derived from various cell types, such as mesenchymal stem cells and immune cells, they possess a biocompatible lipid bilayer that facilitates effective drug encapsulation and delivery. These vesicles enable cell-to-cell communication by transferring bioactive molecules like proteins, lipids, and nucleic acids to target cells. Their small size and ability to cross biological barriers, including the blood-brain barrier, make them ideal for delivering drugs in treating conditions like brain cancer and neurodegenerative disorders. Furthermore, natural exosomes are favored over synthetic carriers due to their low immunogenicity and biodegradability, minimizing the risk of immune rejection and toxicity in therapeutic applications. However, large-scale production and purification of natural exosomes present significant challenges. Standardization of isolation techniques remains an area of ongoing research, with variations in yield and purity across different methods [36]. We have summarized the existing methods in Table 1. Researchers are also investigating ways to enhance the therapeutic efficacy of natural exosomes by modifying their surface properties to increase targeting specificity, which would allow for more precise drug delivery to cancer cells. These advances in natural exosome-based delivery systems could pave the way for more effective treatments in various cancers, including breast and lung cancers [29].

Synthetic exosomes

Synthetic exosomes are engineered to mimic the structure and functionality of natural exosomes, offering several advantages over their natural counterparts, especially in the realm of targeted drug delivery. These exosomes are created through bioengineering techniques that allow for the manipulation of their surface properties, cargo capacity, and targeting abilities. The primary goal of synthetic exosomes is to overcome the limitations associated

Table 1 Isolation methods of natural and synthetic exosomes

Isolation Method	Exosome Type	Yield	Purity	Scalability	Cost effectiveness	Challenges
Ultracentrifugation (UC)	Natural	High (depending on sample size)	High, but can contain contaminants (protein, lipids)	Moderate, requires specialized equipment	Moderate, initial setup cost is high, but operational costs are lower	Time-consuming, labor-intensive, requires large sample volumes, risk of damaging exosomes
Size-exclusion Chromatography (SEC)	Natural & Synthetic	Moderate to High	High	Moderate, requires optimization for large-scale	High operational costs, especially for large volumes	Limited by column capacity, requires high purity of starting material
Filtration-based Methods (e.g., tangential flow filtration)	Natural & Synthetic	Moderate to High	Moderate	Highly scalable, automation available	Moderate to High, depends on system scale	Membrane clogging, need for optimization for large volumes, risk of vesicle loss
Immunoaffinity Capture (e.g., magnetic bead-based methods)	Natural & Synthetic	Moderate to High	High	High, but depends on the antibody specificity	High, reagents and antibody production can be costly	Antibody specificity issues, batch-to-batch variability, potential for incomplete capture
Precipitation based Methods (e.g., ExoQuick)	Natural & Synthetic	Moderate	Low to Moderate	Easy to scale, simple protocol	Low, commercially available kits	Contamination from non-exosomal particles, low purity
Microfluidics based Isolation	Natural & Syntheti	Moderate to High	High	Very High, highly adaptable for automation	High initial investment in technology, but scalable	Requires precise control of fluid dynamics, high complexity
Polymer-based Isolation (e.g., ExoSpin)	Synthetic	Moderate to High	Moderate to High	Moderate to High, scalability can be limited by technology	Moderate to High, depending on the polymer used	Potential contamination, batch variability, sensitivity to variations in sample composition
Density Gradient Centrifugation	Natural	High (especially with optimized gradients)	High	Moderate, requires large centrifugation equipment	High, especially at large scales	Time-consuming, potential contamination with serum proteins, complexity of protocol
Micro- or Nanoparticle-based Isolation (e.g., silica nanoparticles)	Synthetic	High	Moderate to High	Moderate to High, adaptable for various sample types	Moderate, depending on particle costs and technology	Potential aggregation, incomplete isolation, difficulty in scale-up without compromising yield

with natural exosomes, such as variability in production and limited therapeutic payload capacity [37]. By engineering synthetic exosomes, scientists can optimize them to carry a wide range of therapeutic agents, including chemotherapeutic drugs, nucleic acids, and proteins, for specific delivery to diseased cells, especially cancer cells. The synthesis process involves several key steps:

1. **Source Cell Selection**: The first step in synthesizing exosomes is the selection of source cells, which are typically genetically modified to express specific surface markers or receptors that will enhance the exosomes' targeting capabilities. For example, mesenchymal stem cells or tumor cells can be used depending on the desired application.
2. **Exosome Production and Isolation**: Once the source cells are selected, they are cultured in conditions that promote exosome production. The cells release exosomes into the culture medium, which is then collected. Isolation of exosomes is typically achieved through ultracentrifugation, size-exclusion chromatography, or membrane filtration techniques to purify the exosomes and remove contaminants [38] (Fig. 4).
3. **Surface Modification**: After isolation, the surface of synthetic exosomes is modified to improve their targeting abilities. This can be achieved by incorporating specific ligands, peptides, or antibodies onto the exosome membrane. These surface modifications enable synthetic exosomes to recognize and bind to specific cells or tissues, such as tumor cells in cancer therapy. Exosome surface modification techniques have evolved from basic chemical methods to more advanced genetic and physical approaches, significantly enhancing their targeting capabilities, stability, and functionality. Chemical modifications involve click chemistry, bifunctional cross-linkers, and PEGylation to improve drug delivery efficiency. Genetic modifications use engineered donor cells to produce exosomes with specific surface molecules, enabling precise targeting, often seen in fusion protein technology. Physical methods, like electroporation and ultrasonication, are used to load drugs or molecules onto exosome surfaces. Affinity modifications employ aptamers or carbohydrate structures for targeted delivery. Cutting-edge techniques like bioorthogonal reactions, photo-induced modifications, and CRISPR-based editing

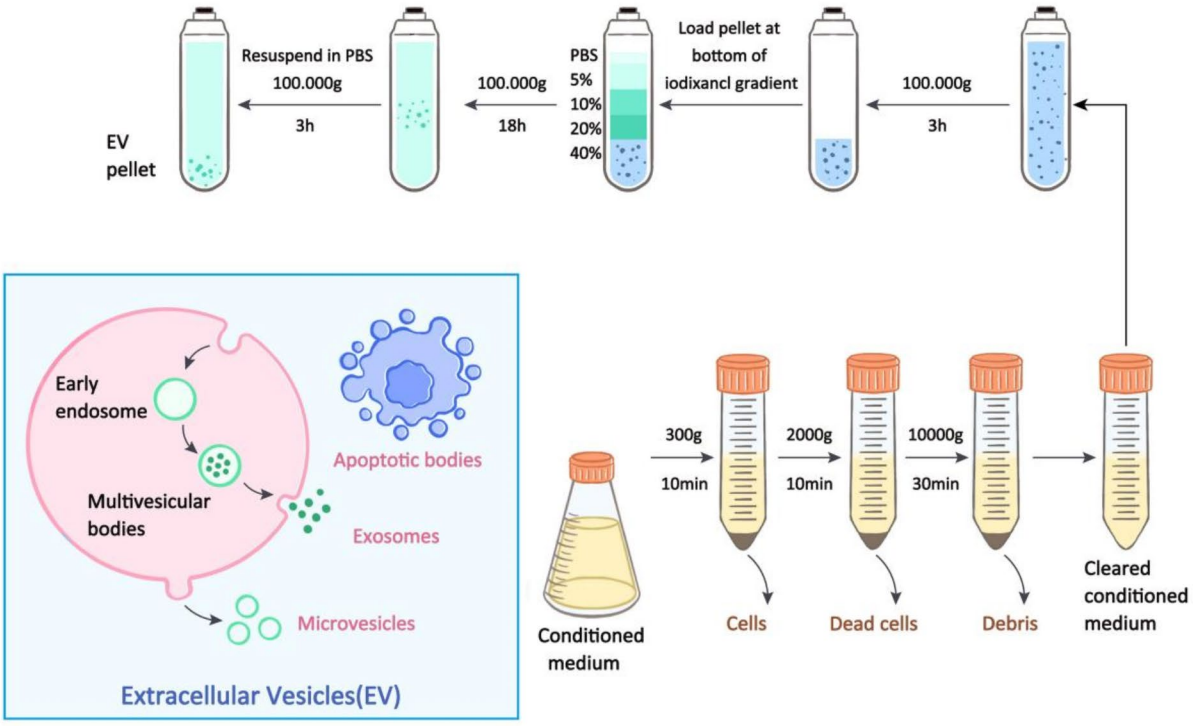

Fig. 4 Exosome Production and Isolation

offer precise, controlled modifications of exosomes, promising further advancements in therapeutic applications, particularly in cancer treatment [39, 40].

4. **Cargo Loading**: One of the key advantages of synthetic exosomes is their ability to carry a wide range of therapeutic agents. Cargo loading can be accomplished through Endogenous Loading Method or Exogenous Loading Method [41] (Fig. 5). In the endogenous loading method, donor cells are modified to produce exosomes that carry therapeutic agents within the cells. This approach includes co-incubation and transfection methods. In the co-incubation method, the drug is incubated with donor cells, and exosomes carrying the drug are released through ILVs. Another common approach is to transfect nucleic acids or proteins into donor cells via chemical or viral vectors, producing exosomes loaded with specific drugs. The advantages of the endogenous method lie in its high safety and specificity, but it is associated with low production efficiency and high cost. The exogenous loading method directly loads drugs into pre-isolated exosomes through permeation techniques. Common methods include co-incubation with drugs, ultrasonic treatment, electroporation, saponin treatment, freeze-thaw, and extrusion. Each method has its pros and cons. For example, ultrasonic treatment temporarily enlarges exosome membrane pores to increase drug permeability, but it may damage the exosome structure. Co-incubation is simple and cost-effective but has relatively low loading efficiency. Electroporation has been extensively utilized to introduce a wide range of druggable molecules into extracellular vesicles (EVs), including nucleic acids like DNA, siRNA, and miRNA, as well as proteins and small molecules [12]. This method is reported to offer enhanced loading efficiency compared to other approaches. Notably, different methods exhibit varying encapsulation efficiency and drug loading capacity depending on the specific cargo being incorporated. For the loading of small molecule drugs, electroporation shows a wide range of efficiency (0.5–50%), indicating its effectiveness depends on specific conditions. Sonication achieves a moderate efficiency of 8–30%, while incubation demonstrates a broader range from 1 to 67%, reflecting considerable variability influenced by various experimental factors [42]. Nowadays, more and more studies have found that the delivery of certain anticancer drugs through exosomes can increase their efficacy. In Wang's study, a recombinant exosome from homologous glioma cells (R-EXO: Recombinant Exosomes) carrying Temozolomide (TMZ) and dihydrotanshinone (DHT) was found to overcome drug resistance and improve lesion-targeting delivery, defined as R-exo-TMZ/DHT (R-EXo-T/D) [43].
5. **Characterization and Quality Control**: After synthesis, synthetic exosomes undergo rigorous characterization to ensure they have the desired size, surface properties, and cargo capacity. Techniques like dynamic light scattering (DLS), transmission electron microscopy (TEM), and nanoparticle tracking analysis (NTA) are used to evaluate size distribution and morphology. Surface modifications are confirmed through techniques like flow cytometry, while the encapsulated cargo is evaluated using high-performance liquid chromatography (HPLC) or mass spectrometry.

One of the key advancements in synthetic exosome development is the ability to modify the exosome surface with targeting ligands or receptors. These modifications can significantly enhance the exosome's ability to home in on specific tissues or tumor sites, ensuring more precise delivery of the therapeutic payload. For example, in breast cancer treatment, synthetic exosomes have been engineered to carry chemotherapeutic drugs directly to tumor sites, reducing systemic toxicity and improving the therapeutic index [44]. In another case, CRISPR/Cas9 technology has been loaded into synthetic exosomes to specifically target cancerous cells for gene editing, offering a potential new approach to treating genetic disorders and certain types of cancers [45].

Additionally, synthetic exosomes have demonstrated significant potential in overcoming one of the main challenges of natural exosomes: large-scale production. Natural exosomes typically have lower yields due to the complexity of their isolation. For example, traditional methods like ultracentrifugation can yield around 440.22 ± 11.71 μg/mL [46]. Synthetic exosomes, or artificial exosomes, can have significantly higher yields. The serial extruding method can yield up to 500-fold higher than natural exosomes [37]. Synthetic exosomes can be produced in a controlled environment with higher yields, making them more suitable for clinical applications. For instance, in pancreatic cancer, synthetic exosomes loaded with siRNA have been shown to effectively silence cancer-promoting genes, resulting in reduced tumor size. Additionally, synthetic exosomes have shown potential in targeting difficult-to-reach areas, such as the brain, by crossing the blood-brain barrier, which is crucial for treating cancers like glioblastoma [47].

Exosome-nanoparticle hybrid systems

Exosome-nanoparticle hybrid systems offer an innovative strategy by combining the natural benefits of

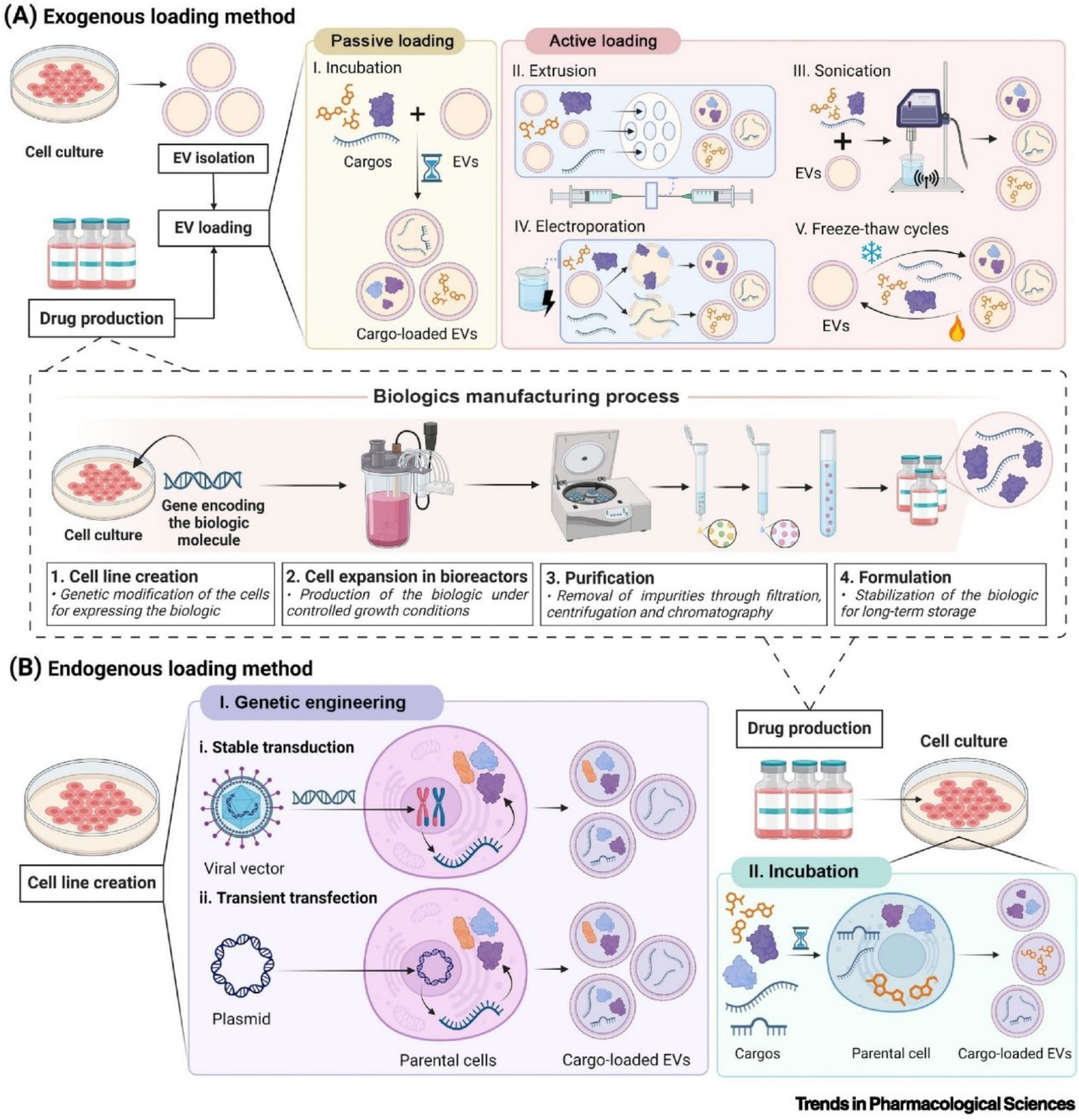

Fig. 5 Extracellular vesicle (EV) loading methods for drug delivery: (**A**) Exogenous Loading Method: EVs are isolated separately, and the biologic drug is produced (steps 1–4). The EVs are then loaded with the drug, which may also be a small synthetic compound. Loading can be passive or active: passive loading involves (I) drug incubation with EVs, while active methods include (II) extrusion, (III) sonication, (IV) electroporation, and (V) freeze–thaw cycles. (**B**) Endogenous Loading Method: This includes (I) genetic engineering and (II) incubation. Parental cells are engineered via (i) stable transduction or (ii) transient transfection. Genetic engineering removes the need for separate biologic drug production and EV loading, combining these processes for efficiency. Once the cell line is established, EV production, isolation, and drug loading are integrated. Incubation involves producing the drug and adding it to the cell culture, similar to the exogenous approach, requiring separate phases. Reproduced from ref. 41 with permission from Elsevier copyright 2024

exosomes with the versatility and enhanced features of synthetic nanoparticles (Table 2). These hybrid systems have been developed to address the limitations of both exosomes and traditional nanoparticle drug delivery systems. By incorporating nanoparticles into or onto exosomes, researchers can create a delivery platform that offers improved stability, targeting specificity, and payload capacity [48]. The use of these hybrids has shown significant potential in cancer therapy, where accuracy

Table 2 Comparison of Natural exosomes, Synthetic exosomes, and Exosome-Nanoparticle Hybrid systems

Feature	Natural Exosomes	Synthetic Exosomes	Exosome-Nanoparticle Hybrid Systems
Source	Naturally secreted by cells, derived from biological fluids or cell cultures	Artificially synthesized, mimicking the structure and function of natural exosomes	Combination of natural exosomes and nanoparticles, nanoparticles encapsulated in exosome membranes
Composition	Lipid bilayer containing proteins, RNA, and other biomolecules	Lipid bilayer, embedded with specific functional components as needed	Nanoparticles as core, coated with exosome membrane, carrying drugs, RNA, or imaging agents
Targeting Ability	Inherent targeting properties inherited from the parent cell	Requires specific ligand or marker modifications for targeting	Combines natural targeting abilities of exosomes with customizable targeting modifications of nanoparticles
Scalability	Difficult to scale up production	Easy to scale up production	Potential for scalability but involves complex preparation
Homogeneity	Highly heterogeneous	High homogeneity	Relatively high homogeneity, depending on control of nanoparticle and exosome sources
Biocompatibility	High biocompatibility, low immunogenicity	Depends on design and composition, potential for immune responses	Retains biocompatibility of exosomes, nanoparticles may add stability or immune response
Cargo Control	Limited to the content of parent cells	Full control over cargo and components	Flexible cargo control by combining the drug-loading properties of nanoparticles with the natural cargo of exosomes
Stability	Susceptible to degradation in vivo	Stability can be enhanced through design	Nanoparticles enhance structural stability, increasing both in vitro and in vivo biological stability
Functional Diversity	Possesses diverse biological activities	Functionalized as needed, lacks natural diversity	Combines the natural biological activity of exosomes with customizable functions of nanoparticles, such as imaging and drug delivery
Challenges	Difficult to achieve consistency and scalability	Complex engineering, potential immune responses	Complex preparation, requires optimization of nanoparticle-exosome integration, potential immune responses and toxicity issues

and effectiveness are crucial. The synthesis process of exosome-nanoparticle hybrids involves several key steps:

1. **Exosome Production**: The initial step in creating an exosome-nanoparticle hybrid involves the production and isolation of exosomes from a suitable source, such as MSCs, tumor cells, or other cell types of interest. Exosomes are harvested using standard isolation techniques, such as ultracentrifugation, size-exclusion chromatography, or immunoaffinity capture methods, to ensure purity and minimize contamination from other vesicles or proteins [49].
2. **Nanoparticle Synthesis**: Simultaneously, the nanoparticles intended for incorporation are synthesized. These nanoparticles can be magnetic (such as iron oxide nanoparticles), gold nanoparticles, or other biocompatible materials. Depending on the desired functionality, nanoparticles may be engineered with specific surface properties or loaded with therapeutic agents like chemotherapeutic drugs or nucleic acids. These nanoparticles consist of both inorganic and organic elements, with each providing distinct characteristics that have an impact on their practical uses and characterization methods. Common inorganic components include metals like gold (AuNPs) and iron oxide (IONPs) nanoparticles, inorganic compounds such as zinc oxide (ZnO) and calcium phosphate (CaP) nanoparticles, as well as porous structures like mesoporous silica nanoparticles (MSNs) and metal-organic frameworks (MOFs). Organic components often consist of polymers, copolymers, lipids, dendrimers, and even isolated cell membranes. Additionally, carbon-based materials such as graphene oxide (GO), fullerene (C60), carbon nanotubes (CNTs), and graphene quantum dots (GQDs) possess properties that bridge the gap between inorganic and organic systems. As a result, while these carbon derivatives can function in both categories, they are often categorized under inorganic materials in hybrid nanosystem design. Together, these diverse materials enable the creation of a vast range of hybrid nanosystems aimed at addressing challenges in the biomedical field [50]. Nanoparticles can enhance the stability of exosomes and protect their cargo from degradation, providing controlled and sustained release properties [51]. Exosomes, with surface proteins such as tetraspanins, integrins, and glycoproteins, inherently possess cell-specific targeting abilities. By combining exosomes with nanoparticles, the targeting capability can be further improved through surface modification with ligands or antibodies. Moreover, exosome-nanoparticle hybrids offer multifunctionality, as they can carry both hydrophilic and hydrophobic drugs, nucleic acids (e.g., siRNA, mRNA), imaging agents, and therapeutic proteins,

enabling multi-modal therapies (such as drug delivery and imaging) within a single system [52].

3. **Hybridization**: The exosome-nanoparticle hybridization process involves combining the isolated exosomes with the synthesized nanoparticles. This can be achieved through physical adsorption, where nanoparticles attach to the surface of the exosomes, or by incorporating nanoparticles into the exosome's lipid bilayer. For more complex systems, nanoparticles can be encapsulated inside the exosome during the cargo loading process. The synthesis methods vary for different types of nanoparticles. For example, gold nanostructures can be synthesized using various physical, chemical, and biological methods, with chemical approaches being the most common for hybrid nanosystems [53]. The synthesis of gold nanostructures requires oxidized gold, a reducing agent, and a stabilizing surfactant to prevent irreversible nanoparticle aggregation. Changes in the identity and concentrations of these reagents will affect the size and morphology of the final nanostructure [54]. AuNPs can be synthesized by reducing chloroauric acid ($HAuCl_4$) with citric acid, which acts as both a stabilizing and reducing agent, with the gold-to-citrate ratio determining the size of the nanoparticles. AuNPs can also be produced through top-down methods like laser ablation, or by "green" synthesis using plant-based reducing agents [55]. Hollow gold nanostructures (AuNSs) are typically synthesized by reducing gold ions on the surface of cobalt nanoparticles, simultaneously oxidizing the core into cobalt oxide. Gold nanorods (AuNRs) can be created by incubating AuNP seeds with silver nitrate ($AgNO_3$), while other non-spherical nanostructures for hybrid systems are commonly synthesized via seed-growth methods using agents such as sodium borohydride ($NaBH_4$) with zwitterionic surfactants, acetic acid with $AgNO_3$, or dilute peptide solutions. Thus, both the geometry and synthesis method can be tailored to specific applications [56]. Liposome formation can be achieved through various methods. In the process of thin-film rehydration, lipids dissolved in an organic solvent or organic/aqueous emulsion are transformed into a film through lyophilization or evaporation. Subsequently, this film is rehydrated and converted into liposomes by means of vortexing, extrusion, or sonication. Other methods for liposome formation include solvent vaporization, ethanol injection, and reverse-phase evaporation [57, 58].
4. **Surface Functionalization**: Once the hybrid is formed, further surface modifications may be applied to enhance targeting. For instance, tumor-targeting ligands or antibodies can be attached to the surface of the hybrid system, enabling the exosome-nanoparticle hybrid to selectively bind to cancer cells while avoiding healthy tissues [59].
5. **Characterization and Testing**: The hybrid system undergoes thorough characterization to confirm that the nanoparticles are successfully incorporated and that the system has the desired size, surface charge, and drug-loading efficiency. Techniques such as TEM, DLS, and NTA are used to assess the size and morphology, while zeta potential measurements confirm surface charge. Drug release profiles are analyzed to ensure controlled and targeted delivery.

One of the key benefits of exosome-nanoparticle hybrids is their enhanced targeting ability. For example, hybrid systems incorporating magnetic nanoparticles allow for the controlled delivery of therapeutic agents to tumor sites through the application of external magnetic fields. This targeting approach has been successfully demonstrated in liver cancer models, where magnetic exosome-nanoparticle hybrids have shown improved drug accumulation at tumor sites, reducing off-target effects and increasing the therapeutic efficacy of chemotherapeutic drug [60]. Similarly, in breast cancer, exosome-nanoparticle hybrids have been engineered to carry doxorubicin, a commonly used chemotherapy drug. The hybrid system guarantees the targeted delivery of drugs to tumor cells, minimizing the damage to healthy tissue and improving patient results [61].

The fusion of exosomes with nanoparticles also allows for the incorporation of a wider range of therapeutic agents, including large and complex molecules such as DNA, RNA, and proteins. This is particularly important in gene therapy applications, where the hybrid systems can protect sensitive nucleic acids from degradation and ensure their delivery to target cells [62]. In a study focused on pancreatic cancer, hybrid exosomes loaded with the chemotherapeutic drug dasatinib showed enhanced uptake by tumor cells and greater inhibition of tumor growth compared to traditional drug delivery systems [38]. These findings underscore the potential of hybrid systems to improve the pharmacokinetics and biodistribution of therapeutic agents, making them more effective in treating aggressive cancers.

Furthermore, hybrid systems offer the advantage of combining different therapeutic strategies within a single platform. For instance, in GB, hybrid exosomes incorporating both magnetic nanoparticles and chemotherapeutic drugs have been used to simultaneously target tumor cells and enhance the penetration of drugs into the brain. This multi-functional approach not only improves the delivery of drugs to hard-to-reach areas but also enhances the overall therapeutic effect, offering

new hope for patients with otherwise difficult-to-treat cancers.

The choice between exosomes alone and hybrid nanosystems will depend on the specific therapeutic goals, scalability requirements, and cost considerations. If the goal is to leverage the natural biocompatibility, low immunogenicity, and ability to carry a wide variety of cargo, exosomes alone may be preferred for specific, personalized, or precision therapies. Such as using in treating Duchenne muscular dystrophy by leveraging the natural regenerative properties of cardiosphere-derived exosomes [63]. However, scaling exosome production and improving the consistency of cargo loading remain significant challenges. If the focus is on improving scalability, production efficiency, and the ability to better control cargo loading and release, hybrid nanosystems may be the best route forward. By combining the biological benefits of exosomes with the versatility and scalability of synthetic nanoparticles, hybrid systems could potentially overcome many of the current limitations of exosome-based therapies. These systems could also offer synergistic effects, such as improved targeting and enhanced drug delivery efficiency [64]. In the long term, hybrid nanosystems may offer a more practical and scalable solution for therapeutic applications, particularly when considering the need for mass production, cost-effectiveness, and control over the therapeutic outcome. However, careful consideration must be given to the selection of materials, potential immunogenicity, and the complexity of formulation to ensure that hybrid systems can be effectively translated into clinical use.

To address the yield and scalability issues, the next major step should be the development of high-yield, automated production systems. Bioreactor-based systems that can cultivate cells at a large scale and enhance exosome production need to be optimized. Recent advances in 3D cell culture and microfluidic devices are promising as they allow for more controlled and efficient exosome secretion. These systems can potentially improve the consistency of exosome production and make the process more scalable [65, 66]. Moreover, automation of exosome isolation using systems like microfluidics or centrifugal filtration could increase efficiency and reduce labor costs. Technologies that minimize handling time and reduce manual interventions would also help mitigate batch-to-batch variability [67]. Genetic engineering of cells to enhance exosome production is an exciting avenue for overcoming yield limitations. Techniques like CRISPR/Cas9 and viral transfection can be used to modify the donor cells to increase exosome secretion, modify the cargo content, or target specific molecules to improve therapeutic efficacy. For example, engineering cells to produce exosomes that are enriched in specific miRNAs, proteins, or therapeutic RNA could allow for more effective treatments [68]. Additionally, using induced pluripotent stem cells (iPSCs) or immortalized cell lines as consistent, scalable sources of exosomes could help overcome the limitations posed by primary cells, which often have variable production rates and require extensive maintenance [69].

Applications in cancer therapy

Respiratory system

Lung cancer is the most common and deadliest malignant tumor of the respiratory system, holding a central role among respiratory tract cancers. It ranks first globally in terms of both incidence and mortality. Lung cancer is primarily divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for about 85% of cases. Due to its high prevalence and poor prognosis, lung cancer is one of the most difficult challenges in respiratory oncology [70]. Lung cancer development and progression is a complex, multi-step process involving genetic and environmental factors, as well as changes in intracellular molecular pathways [71].

In lung cancer treatment, traditional chemotherapy drugs like paclitaxel are commonly used for their ability to stabilize microtubules, stopping mitosis and killing cancer cells. However, paclitaxel's lack of selectivity can also harm healthy cells, particularly in the liver and kidneys. This non-specificity often results in severe systemic toxicity with side effects such as nausea, hair loss, immunosuppression, neurotoxicity, and liver dysfunction, complicating treatment and limiting tolerable dosages. To overcome these challenges, recent studies have explored using exosomes as drug carriers. Due to their robust structure and distinctive penetration mechanism, exosomes are regarded as promising drug delivery vehicles capable of transporting proteins, DNA, RNA, and various pharmaceutical agents [72]. Research has shown that loading paclitaxel into exosomes not only significantly reduces off-target toxicity but also enhances the drug concentration in cancer cells, thereby improving therapeutic efficacy. Moreover, exosome-loaded paclitaxel (ExoPAC), delivered through either oral or intravenous routes, has been shown to increase bioavailability and tumor specificity [73]. Notably, a functionalized exosome system, FA-ExoPAC, which targets folate receptors (FRα) overexpressed in cancer cells like lung tumors, has demonstrated impressive results. In animal models, oral FA-ExoPAC achieved a tumor inhibition rate of 55%, while intravenous administration of FA-ExoPAC surpassed the efficacy of Abraxane (albumin-bound paclitaxel), which is FDA-approved for similar use. Compared to traditional intravenous paclitaxel, exosome-loaded paclitaxel not only improves drug delivery efficiency but also significantly reduces toxicity [74]. Studies have

shown that animals treated with exosome-loaded paclitaxel experienced no significant immunosuppression or systemic toxicity, with liver and kidney function remaining unaffected. This marks a stark contrast to the adverse effects typically observed with conventional paclitaxel treatments, highlighting the potential of exosome-based drug delivery systems for safer and more effective cancer therapies [75] (Fig. 6).

Exosomes hold significant promise in enhancing the effectiveness of radiotherapy, particularly in overcoming radioresistance, which poses a major challenge in lung cancer treatment. Research has shown that Exo-associated miRNAs can reduce radioresistance. For instance, Exo-miR-26b-5p has been found to suppress ATF2 expression in lung tissues, thereby increasing radiosensitivity and promoting apoptosis in cancer cells [76]. Additionally, Exo-miR30a has the ability to suppress ATF1 expression and disrupt the ATM pathway, which plays a essential role in recognizing the DNA damage response (DDR). By doing so, Exo-miR30a impairs DNA strand repair and induces apoptosis in tumor cells. Furthermore, the upregulation of Exo-miR-208a and Exo-miR-1246 in tumor cells has been shown to enhance their sensitivity to radiotherapy [77–79]. Exosomes can also diminish radioresistance by stimulating the production of reactive oxygen species (ROS), which effectively destroy tumor cells during radiation therapy [80].

Exosomes hold promise as potential agents for immunotherapy. They have been utilized to deliver signals, like MHC class I/peptide complexes, to immune cells like undeveloped dendritic cells (DCs). This leads to the activation of $CD8^+$ T-cells, which in turn enhances the immune reaction, facilitates the elimination of tumor cells, and induces the formation of memory T-cells [81]. In exosome-based lung cancer immunotherapy, cell-free vaccines are a key research focus due to their ability to induce lasting and specific immunity that targets and kills cancer cells. Exosomes from dendritic cells can act as a

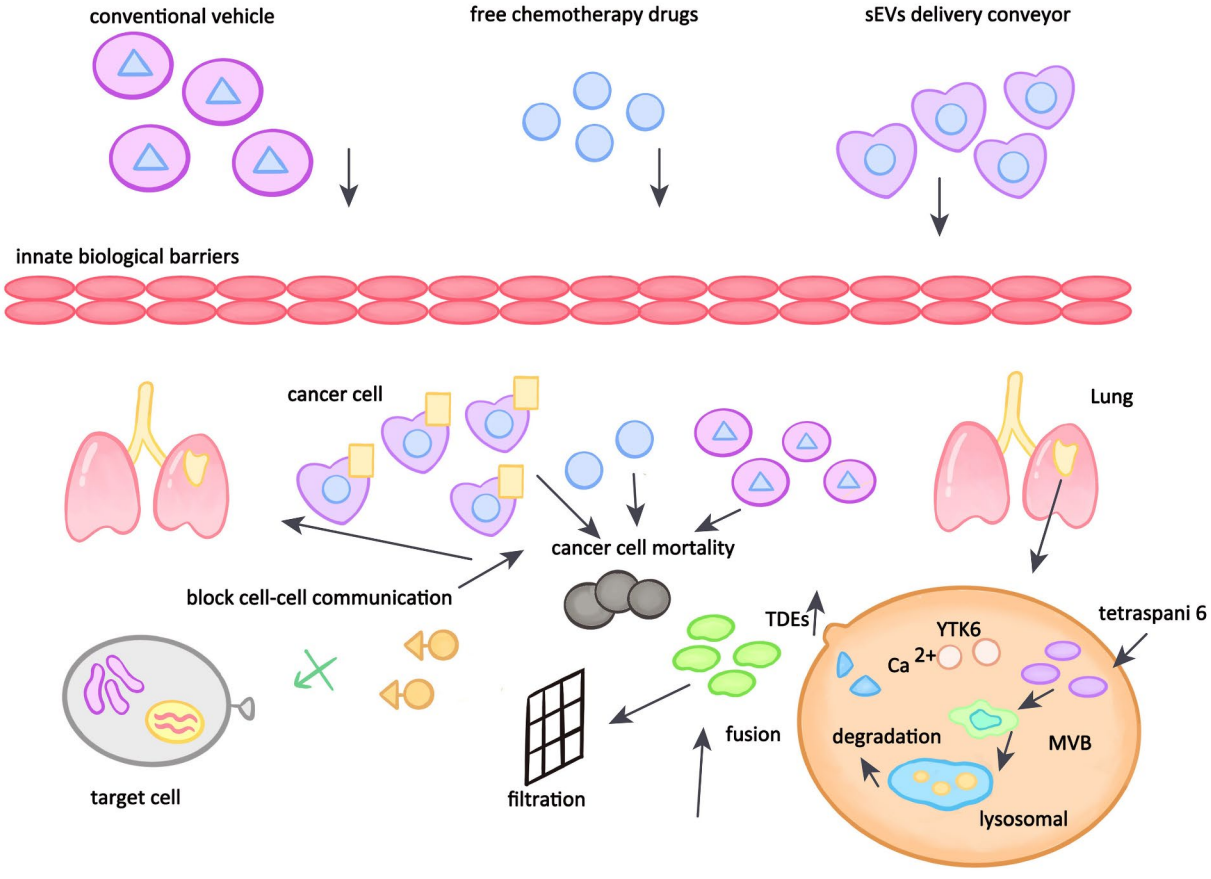

Fig. 6 sEVs in anti-cancer therapy. Depleting tumor-derived exosomes (TDEs) through methods like inhibiting their production, filtering them from circulation, or blocking their interaction with cells could disrupt neoplastic progression. sEVs also serve as effective drug delivery vectors. With enhanced permeability and retention (EPR) effects, the ability to traverse biological barriers, and reduced immunogenicity, sEVs can efficiently deliver anticancer medications to target cells for both single therapy and combination therapy. Reproduced from ref. 75 with permission from Elsevier copyright 2021

nanovaccine platform by delivering patient-specific neoantigens to lymph nodes, activating antigen-presenting cells. This process enables T and B cells to recognize and attack tumor cells, triggering a broad-spectrum immune response. Research has shown that this exosome-based nanovaccine can effectively inhibit tumor growth, while enhancing tumor-specific immune memory to delay tumor recurrence and metastasis [82]. Gustave Roussy and Curie institutes have developed an immunotherapy involving metronomic cyclophosphamide (mCTX) followed by vaccinations with tumor antigen-loaded dendritic cell-derived exosomes (Dex). A Phase II study evaluated the efficacy of Dex vaccines combined with mCTX for the treatment of NSCLC. The results demonstrated that the Dex vaccine effectively activated NK cells, thereby enhancing the anti-tumor immune response (NCT01159288) [83]. The core mechanism lies in the exosomes' ability to efficiently transport antigens and sustain antigen presentation, thereby strengthening the immune system's targeted response against tumors. Additionally, studies have shown that plant-derived nanovesicles can transfer mitochondrial DNA to tumor-associated macrophages, activating the cGAS-STING pathway. This reprograms macrophages and boosts anti-tumor immune responses. In lung cancer models, this mechanism not only suppresses tumor growth but also significantly enhances the efficacy of PD-L1 inhibitors [84]. Furthermore, encapsulating IL-12 mRNA in exosomes for inhalable delivery allows for targeted treatment of lung cancer cells while minimizing systemic side effects. The expression of IL-12 activates immune cells within the tumor microenvironment, strengthening the anti-tumor immune response and fostering long-lasting tumor-specific immune memory [85].

Combining chemotherapy with immunotherapy has been used in lung cancer treatment [86]. Olejarz et al. showed that combining exosomes loaded with anti-angiogenic chemotherapeutics and PD-1/PD-L1 inhibitors can substantially reduce treatment resistance [87]. Gene therapy provides an alternative strategy to address therapy resistance. Medicinal RNAs and chemotherapy drugs enclosed in exosomes have shown promising tumor-suppressing effects. For example, exosomes carrying Doxorubicin (Dox) and miR-21 inhibitors have been found to significantly reduce tumor volume [88]. The combination of radiotherapy and immunotherapy can also be facilitated using exosomes. Upon exposure to 8 Gy irradiation, lung cancer cells were found to overexpress CDCP1, an ideal tumor-associated antigen (TAA). Exosomes can then deliver these overexpressed TAAs to DCs, promoting the aggregation, infiltration, and activation of $CD4^+$ and $CD8^+$ T cells to enhance tumor destruction. In summary, compared to monotherapy, combination cancer therapies offer improved treatment outcomes [89, 90].

Exosomes, as natural nanocarriers, demonstrate great potential in lung cancer therapy. However, they also face several unique challenges, primarily arising from the distinctive biological characteristics of lung cancer and the tumor microenvironment (TME). One unique challenge in lung cancer treatment is the physiological barriers of the lungs, especially in the context of the highly gas-exchange environment, which complicates drug delivery. Lung tissue exhibits high biological barrier properties, particularly around tumor tissues, where the blood-air barrier (BAB) and blood-lung barrier (BLB) hinder the effective delivery of exosomes to the tumor site. In lung cancer, small blood vessels, pronounced ventilation-perfusion mismatches, and high airflow in the airways further impede exosome penetration. Compared to other tissues, the physiological environment of the lungs may lead to rapid clearance or misdirection of exosomes before they reach the tumor site, thereby reducing their therapeutic efficacy [91]. TME of lung cancer exhibits strong immune evasion characteristics. Common features of the immunosuppressive environment in lung cancer include tumor-infiltrating immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, as well as the overexpression of immune checkpoint molecules like PD-1/PD-L1. Additionally, TAMs exert inhibitory effects on immune cells. Although exosomes hold potential in immune modulation, they face significant challenges within the immunosuppressive environment of lung cancer. For instance, exosomes may be phagocytosed by immunosuppressive cells or rejected via the PD-1/PD-L1 pathway, reducing their activity and targeting efficacy at the tumor site. The immune evasion mechanisms of lung cancer complicate the use of exosomes as vectors for immunotherapy [92, 93]. To overcome the unique challenges in applying exosomes for lung cancer treatment, modifications can be made to the surface of exosomes to enhance their affinity for lung cancer-specific receptors (e.g., EGFR, PDGFR, VEGFR) or tumor markers (e.g., KRAS mutations, p53 mutations). For instance, the surface of exosomes can be decorated with anti-EGFR monoclonal antibodies or specific peptides to improve targeting, thereby facilitating their localization and entry into lung cancer cells [94]. Additionally, to enhance the ability of exosomes to traverse pulmonary barriers, certain chemical agents that promote membrane fusion or gene engineering techniques can be used. Tumor-targeting peptides, such as iRGD, have demonstrated an ability to increase the penetration of exosomes into tumor tissue [95]. Furthermore, exosomes can be employed as carriers for immune-modulatory molecules to counteract immune evasion mechanisms in lung cancer. By delivering immune checkpoint inhibitors (e.g.,

anti-PD-1, anti-PD-L1 antibodies) or cytokines (e.g., IL-2, IFN-γ), exosomes can boost immune cell responses against tumors. They can also effectively modulate the tumor microenvironment, activate T cells, inhibit Tregs, and reduce the accumulation of MDSCs [96].

Digestive system

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-associated deaths worldwide [97–99]. Although there have been considerable advances in surgical techniques, endoscopic procedures, chemotherapy, radiotherapy, and targeted therapies, the prognosis for patients with advanced GC remains poor, placing a heavy burden on both families and society. Therefore, it is urgent to find more effective treatment methods [100]. Exosomes, as an innovative drug delivery system, are utilized to transport biomolecules and chemotherapy agents in cancer treatment. MSCs can enclose and transport paclitaxel to target cells via exosomes, exhibiting significant anticancer effects [101]. Exosomes act as nanoparticles to transport anti-miR-214, effectively reversing GC's resistance to cisplatin. This approach shows promise as an alternative for treating cisplatin-refractory GC [102].

Cisplatin is among the highly potent and commonly used chemotherapy treatments for advanced GC. Exosomes derived from cisplatin-refractory GC cells carry miR-500a-3p, targeting FBXW7 in both in vitro and in vivo models, thereby boosting cisplatin tolerance and promoting the stem-like properties of GC cells [103]. However, certain studies have indicated that external anti-214 can overcome cisplatin tolerance in GC cells and inhibit tumor progression. Exosome-released miR-107 substantially enhances the sensitivity of chemotherapy-resistant GC cells by targeting the HMGA2/mTOR/P-gp pathway [104]. Exosomes from macrophages can act as vehicles to transport miR-21 inhibitors to GC cells, promoting cell migration while preventing apoptosis. In comparison to traditional transfection techniques, exosome-based delivery of miR-21 inhibitors exhibits stronger inhibitory effects and lower cytotoxicity, emphasizing the promise of miR-21 and exosomes as therapeutic tools for gastric GC [105]. Since exosomes can carry tumor antigens to activate CTLs, they hold promise for use in cancer immune therapy. Exosomes from tumor cells could serve as a new type of cancer vaccine. Heat-treated malignant ascites-derived exosomes have demonstrated the ability to promote DC maturation and trigger a tumor-targeted CTL response, suggesting that heat stress can boost the immunogenicity of malignant ascites exosomes in patients with GC [106]. Nevertheless, tumor-derived exosomes (TDEs) contain various oncogenes that can drive tumor growth, making TDE-based vaccine safety uncertain. DC vaccines can be quickly targeted and destroyed by antigen-specific CTLs. In contrast, exosomes from DCs display both MHC-I and MHC-II molecules, boosting T-cell mediated immune response and tumor elimination. Due to their longer lifespan than DC vaccines, DC-derived exosomal vaccines are being considered as a potential alternative to traditional DC vaccines [107].

In 2020, approximately 906,000 people globally were diagnosed with liver cancer, most commonly hepatocellular carcinoma (HCC). HCC is the third most common cause of cancer deaths worldwide, with a five-year survival rate of only about 18% [108]. The primary treatments for HCC consist of surgery, liver transplantation, localized radiation or chemotherapy, and combination therapies [109]. HCC has a subtle onset and lack of early markers, and current treatments like RFA, TACE and sorafenib have limitations [110]. Thus, identifying early diagnostic indicators for HCC and addressing issues such as treatment resistance and disease relapse are urgent priorities in medical practice. The growth and advancement of HCC involve highly complex pathological processes, with the underlying molecular mechanisms still not fully understood. Numerous preclinical and medical studies have demonstrated that virus-induced infections, as well as alcohol-related and non-alcohol liver damage, are major contributors to HCC, though its precise disease mechanism remains unclear [111]. In recent times, both in lab and in living organisms' studies have revealed that exosomes might play an essential role in the initiation, progression, diagnosis, and treatment of HCC [112]. This could offer a new approach for treating HCC.

Drug unresponsiveness or tolerance to different chemotherapy drugs is a major challenge in HCC treatment. Sorafenib, a primary targeted therapy for HCC, has been demonstrated in numerous clinical trials to effectively extend patient survival with advanced stages of the disease. However, many patients develop resistance to sorafenib, with studies suggesting that exosome-mediated suppression of apoptotic signaling and the promotion of epithelial-mesenchymal transition (EMT) play a role in this treatment resistance [113]. Zhen et al. discovered that exosomes released by HCC cells with high resistance activate the hepatocyte growth factor (HGF)/c-MET/Akt pathway, thereby reducing sorafenib-triggered apoptosis [114]. Takahashi et al. discovered that drug therapy could increase exosomal linc-RoR levels in HCC cells, which inhibits p53 level and diminishes sorafenib-triggered apoptosis [115]. Upon sorafenib treatment, exosomal linc-VLDLR levels in HCC cells increase. This linc-VLDLR is subsequently transferred to neighboring cells through exosomes. After being absorbed by target cells, linc-VLDLR causes drug resistance by increasing ATP-binding cassette sub-family G member 2 (ABC-G2) [116].

One of the key mechanisms behind multidrug resistance (MDR) in tumor cells is their ability to actively expel anticancer drugs from the cells. In HCC cells exhibiting MDR, the expression of P-glycoprotein-1 (Pgp-1/ABC-B1) is increased, contributing to the development of drug resistance [117]. In vitro and in vivo studies have indicated that exosomes, functioning as drug carriers, are capable of bypassing the Pgp-1-mediated efflux system and effectively delivering drugs to tumor cells. This advantage is associated with the distinctive uptake mechanisms of exosomes [118]. The effectiveness of exoDOX, exosomes loaded with doxorubicin, is comparable to doxorubicin treatment alone, but exoDOX significantly reduces the cardiotoxicity typically associated with doxorubicin [119]. This suggests that exosomes, as drug carriers, exhibit a degree of targeting capability. Connexin protein Cx43 (connexin 43) may play a role in facilitating this targeting capability [114]. Rivoltini et al. used lentiviral transfection to introduce exogenous rhTRAIL into K562 cells. The exosomal rhTRAIL from these cells successfully triggered apoptosis in various malignant tumor cells, including HCC, in both in vivo and in vitro studies, without notable toxicity to normal cells [120]. Liang et al. used electroporation to introduce miR-26a into exosomes derived from kidney cancer cells. The exosomes were efficiently absorbed by HepG2 cells, resulting in the downregulation of Cyclin D2, Cyclin E2, and CDK6. This, in turn, induced cell cycle arrest in HCC cells, inhibiting their proliferation and metastasis [121]. Adipose tissue-derived mesenchymal stem cells (AMSCs) expressing miR-122 can increase HCC drug sensitivity by delivering exosomal miR-122 to HCC cells, leading to G0/G1 cell cycle arrest and apoptosis [122]. Furthermore, When Huh7 cells with increased miR-122 are cocultivated with HepG2 cells with low miR-122 levels, the exosomal transfer of miR-122 between the cell lines significantly raises miR-122 in HepG2 cells. This effectively inhibits the growth rate and aggressiveness of HepG2 cells [123]. Studies indicate that IGF-1R could be a target of exosomal miR-122, affecting HCC drug sensitivity by modulating IGF-1R levels [124]. Wang et al. enhanced within-tumor levels of miR-335-5p by directly injecting small amounts of miR-335-5p-loaded exosomes, which exhibit anti-tumor effects. This approach effectively halted tumor growth by downregulating thrombospondin 1 and G-protein signaling 19 expressions [125]. Zhang et al. administered exosomes carrying miR-320a to rats through tail vein injection, effectively inhibiting HCC growth and spread by downregulating pre-B-cell leukemia homeobox 3 in the rats [126]. Thus, both intratumoral and intravenous (i.v.) injection are effective pathways for exosome-based drug delivery, offering a solid conceptual foundation for future medical applications.

While exosomes can help HCC cells evade immune system monitoring, they also possess strong immunogenicity and can trigger immune reactions. As an immune-stimulating substance, exosomes demonstrate a significantly stronger immune activation effect compared to cell lysates [127]. For instance, the plentiful AFP in exosomes derived from HCC cells cultured in vitro can enhance antigen presentation capability of DCs, activate $CD8^+$ T cell growth, modulate cytokine secretion (by decreasing IL-10 and TGF-β while elevating IFN-γ and IL-2), and promote immune-triggered apoptosis [128]. Comparable outcomes have been noted in in vivo studies. For instance, injecting AFP-containing exosomes derived from DC cells (DEXAFP) into mice with primary HCC triggered a robust targeted immune reaction, promoted the accumulation of $CD8^+$ T cells in tumors, and diminished the tumor expansion speed [129]. Injecting exosomes from fat-derived mesenchymal stem cells into HCC mice through the tail vein improved the natural killer (NK) cells' ability to inhibit tumor expansion [130]. The liver's immune-tolerant nature poses challenges for HCC immune therapy. However, exosomes can evade the liver's immune-suppressive environment, showcasing significant advantages in this context [131]. Chemotherapy drugs can cause HCC cells to release exosomes with heat shock proteins (HSPs), including HSP60, HSP70, and HSP90, which stimulate human NK cell cytotoxicity, resulting in anti-tumor effects. Even in the presence of drug-resistant agents, such as carboplatin and irinotecan hydrochloride, HCC cells can still release HSP-containing exosomes. These exosomes increase the level of proteins like CD69, NKG2D, and NKp44 in NK cells, while downregulating the suppressive receptor CD94. Additionally, they increase granzyme B production, thereby enhancing the cytotoxic response of NK cells [132]. Therefore, these drug-induced exosomes hold potential as a novel HCC treatment vaccine.

Pancreatic cancer ranks as the sixth deadliest cancer worldwide, according to statistics. The most prevalent form of the disease is pancreatic ductal adenocarcinoma (PDAC) [133]. PDAC is notoriously challenging to treat, with a five-year survival rate of less than 10% [134]. Therefore, new therapies in PDAC are urgently [135]. While liposomal nanoparticles (LNPs) are widely used, they are ineffective for treating solid tumors due to poor tissue penetration and inability to cross physiological barriers. In contrast, viral vectors transport efficiently but are strongly immunogenic [136, 137].

EVs are promising options for gene transfer due to their low immune response and cell toxicity, as well as their ability to cross physiological barriers [31]. Chiang CL et al. present readily expandable, dual-targeted therapeutic extracellular vesicles (dtEVs) loaded with large copy quantities of TP53 mRNA or $siKRAS^{G12D}$, capable of

effectively suppressing substantial solid PDAC tumors. Their dtEVs are engineered with a CD64(Fc-gamma receptor 1) protein on their surface, modified at the N-terminus with a CKAAKNK (CK) tissue-homing peptide, specifically designed to target pancreatic tumor tissue [138]. This engineered protein, CD64CK, functions as a general anchor that binds with high affinity to any clinically available therapeutic humanized monoclonal antibodies (hmAb), forming an additional targeting ligand on the EV outer layer. They utilize humanized anti-receptor tyrosine kinase-like orphan receptor 1 (αROR1, clone: 2A2) antibodies as the additional ligand, specifically targeting ROR1 receptors, which are typically found on tumors but absent in normal tissues [139, 140]. Plasmid DNAs encoding the CD64CK protein and either TP53 mRNA or siKRAS^{G12D} are sequentially introduced into mouse embryonic fibroblast (MEF) cells or human bone marrow stem cells (hBMSCs) using Transwell®-based asymmetric cell electroporation (TACE). This method using Transwell® inserts for sequential delivery of plasmid DNA leads to EVs secretion, and their combination with Gemcitabine effectively inhibits tumors and spreads in mice, prolonging survival by inducing multiple effects. This study showcases an easy, cost-effective method for producing plentiful targeted EVs loaded with high levels of genetic cargo, demonstrating their potential for effectively treating advanced cancers in animal models [141].

Researchers developed an exosome-based dual delivery system to enhance immunotherapy for PDAC. This system utilizes bone marrow MSC-derived exosomes to carry oxaliplatin (OXA) and galectin-9 siRNA, inducing immunogenic cell death (ICD) in tumor cells and reversing the immunosuppressive tumor microenvironment. Experimental results showed that this dual delivery system not only significantly improved drug tumor-targeting and cellular uptake efficiency but also enhanced the anti-tumor immune reaction, suppressed tumor growth, and extended the survival of mice, demonstrating its great promise in the treatment of PDAC [142]. In addition, the first clinical-grade exosomes derived from MSCs, loaded with siRNA targeting the Kra^{sG12D} mutation, were introduced as a potential therapeutic approach for PDAC in animal models. These engineered exosomes effectively targeted the Kras^{G12D} mutation in PDAC cells in vivo, demonstrating a notable improvement in overall survival without causing toxicity. Furthermore, this innovative strategy has progressed to a Phase I clinical trial for PDAC patients harboring the Kras^{G12D} mutation (NCT03608631) [143].

Based on recent cancer data, colorectal cancer (CRC) ranks third most common and the second deadliest cancer globally. Despite progress in surgical methods and the extensive use of supplementary chemotherapy, the mean five-year survival rate for CRC patients remains around 65%. Nonetheless, the prognosis still poor for patients with advanced metastases or unresectable tumors, with a five-year survival rate as low as 15% [144]. 5-FU-based chemotherapeutic treatment is a crucial component in treating CRC. However, its therapeutic efficacy is significantly compromised by multidrug resistance (MDR) that can develop with prolonged administration of 5-FU. Several mechanisms contribute to cancer cell resistance to chemotherapy drugs and studies on miRNAs' role in this resistance have revealed various findings and demonstrated possible countermeasures [145]. Hence, researchers hypothesize that the co-administration of MDR-reversing miRNAs and anticancer drugs will be a potential approach to get over MDR in cancer chemotherapy [146, 147]. Nonetheless, a secure and effective targeted transport system is crucial for effective CRC treatment.

Herein, Gaofeng Liang et al. created a method to generate targeted exosomes for co- transport of a miR-21 inhibitor (miR-21i) and anticancer agents into 5-FU-resistant HCT-116 (HCT-116^{5FR}) cells, a colorectal cancer cell line with high miR-21 expression. To enhance the targeting ability of exosomes, they utilized Her2—a membrane protein widely participating in tumor growth and inhibition—as a specific tumor-homing polypeptide for targeting tumor cells. To efficiently direct the exosomes to HCT-1165FR cells, they fused Her2 with LAMP2, which allowed the Her2-LAMP2 fusion protein to be displayed on the exosome surface, thereby facilitating targeted uptake via EGFR receptor- driven endocytosis in HCT-116 cells. Engineered 293T cells were used to produce target-specific exosomes in large quantity. Drug packaging involved mixing 5-FU with the exosomes via electroporation, followed by co-incubation with miR-21i to form the co-delivery system (target-Her2-LAMP2-GFP, THLG-Exo/5-FU/miR-21i, as depicted in Fig. 7). These engineered exosomes (THLG-Exo) were subsequently assessed for their targeting capability and treatment effects, both in vitro and in vivo. The engineered exosomes caused cell cycle halt, enhanced apoptosis, and inhibited cancer cells proliferation more effectively compared to the single-agent therapy with either miR-21i or 5-FU alone. Overall, the co-delivery of miR-21i and 5-FU using the engineered THLG-Exo resulted in a synergistic effect that effectively reversed drug resistance in colorectal cancer cells. The combination therapy significantly enhanced cytotoxicity in the drug-resistant cells compared to either agent used alone. These findings suggest that this exosome-based delivery system holds substantial potential for enhancing the efficacy of conventional chemotherapy, particularly in drug-resistant cancers [148]. Moreover, it has been demonstrated that curcumin can interfere with colon carcinogenesis in multiple chemical and genetic rodent models. And, it has been revealed

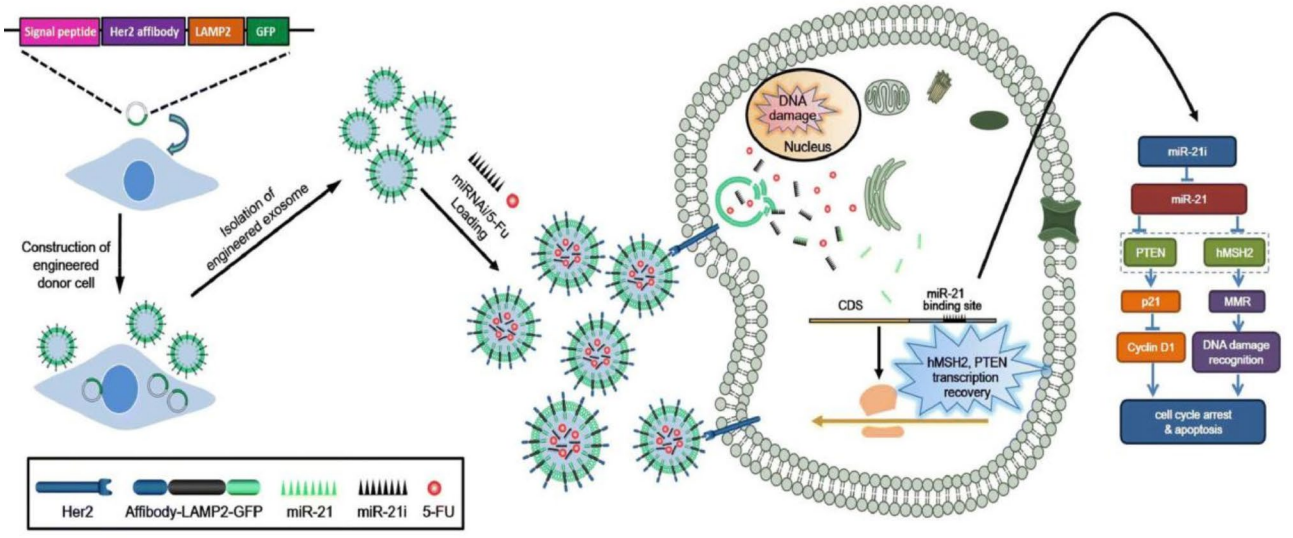

Fig. 7 Engineered exosomes based nanocarrier for 5-FU and miR-21i simultaneously deliver to HCT-116^{5FR} human colon cancer cells for enhancing chemotherapy efficacy. Reproduced from ref. 148 with permission from Springer Nature copyright 2020

that curcumin has a potent inhibitory impact on the growth of colon cancer cell lines. James Graham Brown Cancer Center initiated a phase I clinical trials to test the therapeutic effect of plant exosomes on colon cancer (NCT01294072) [149].

The first unique challenge faced by digestive system tumors is the physiological barrier of the gastrointestinal tract, particularly the presence of gastric acid, digestive enzymes, and the intestinal barrier. These factors not only affect the stability of exosomes but also limit their bioavailability in the gut. In this environment, exosomes must be able to withstand harsh conditions such as gastric acid and pancreatic enzymes to avoid degradation before reaching the tumor target [150]. Additionally, digestive system tumors often exhibit a distinct gut immune microenvironment, where TAMs, Tregs, and MDSCs play a critical role in immune evasion within the gut [151]. The gut microbiota also significantly impacts tumor immune escape, adding complexity to the immune modulation required for digestive system tumor treatments. Moreover, digestive system cancers, especially colorectal and pancreatic cancers, often display resistance to chemotherapy and targeted therapies. This resistance may arise from tumor heterogeneity, resistance genes (such as KRAS mutations, PI3K/Akt/mTOR pathway activation), and the hypoxic, acidic tumor microenvironment, as well as the presence of drug efflux pumps [152, 153]. Furthermore, digestive system tumors are typically characterized by abundant blood supply and a complex tumor microenvironment, where low oxygen levels, acidic conditions, and stromal factors hinder the penetration of exosomes into the tumor, further complicating treatment [154]. To address the challenges in applying exosomes for digestive system tumors, several strategies can be employed. First, gastrointestinal stabilization can be achieved by encapsulating exosomes or combining them with acid- and enzyme-resistant materials [such as polyethylene glycol or gastrointestinal agents] to enhance their stability and transport efficiency in the digestive tract. Additionally, to improve targeted delivery, exosomes can be surface-modified with specific receptors that target gastrointestinal epithelial cells or use molecules that promote cellular uptake [151]. Furthermore, to enhance the effectiveness of immunotherapy, exosomes can be combined with immune cells, such as dendritic cells or T cells. This approach can boost immune cell recognition and cytotoxicity against digestive system tumors, thereby improving therapeutic outcomes [155].

Cardiovascular system

Chronic Myelogenous Leukemia (CML) is a type of myeloproliferative neoplasm marked through the reciprocal translocation t[9;22][q34;q11] [156]. A significant shift in CML treatment occurred during the early 1990s following the identification of Imatinib mesylate (IM), which became the primary therapy for patients because of its targeted inhibition of Bcr-Abl protein tyrosine kinase activity. The targeted therapy has increased the ten-year survival rate of patients from around 20% to 80–90% [157]. For patients who do not respond to

standard treatment, several second-generation (dasatinib and nilotinib) and third-generation [bosutinib and ponatinib] tyrosine kinase inhibitors (TKIs) have been created in recent decades and are currently widely utilized in CML therapy [158].

Although TKIs have proven highly effective in the treatment of CML, the emergence of drug resistance limits their treatment promise. This challenge is additionally exacerbated by the requirement for increased dosages, which can lead to prolonged side effects, including cardiac toxicity, disrupted bone and mineral metabolism, and hypothyroidism [159, 160].Developed resistance can arise from various mechanisms, such as Bcr-Abl protein overexpression or mutations within the BCR-ABL gene that reduce Imatinib attachment [161]. Nucleic acid inhibitors targeting gene expression, such as RNA interference (RNAi), have been suggested as a strategy to target neoplastic cells for treating CML [162, 163]. However, the application of RNA-centered therapies has been limited due to insufficiently effective transport methods [164]. An optimal therapeutic conveyance system ought to effectively target specific cell types, thereby enhancing therapeutic efficacy while minimizing toxicity. Among transport systems, liposomes—artificial vesicles composed of a lipid bilayer—are the most extensively studied, particularly for their applications in cancer therapy [165].

Phatsapong Yingchoncharoen et al. developed engineered exosomes for targeted delivery of Imatinib or BCR-ABL siRNA to CML cells, aiming to get over drug tolerance. The interleukin-3 receptor (IL3-R) is known to be excessively expressed in CML and acute myeloid leukemia (AML) blasts, while it shows minimal or no expression in normal hematopoietic stem cells, indicating that IL3-R could be a potential receptor site for an exosome-based drug delivery system to suppress BCR-ABL. They demonstrate that engineered exosomes containing IL3-Lamp2B, loaded with Imatinib, can selectively target tumor cells in vivo, resulting in a reduction in tumor size. Moreover, these modified exosomes effectively transport effective BCR-ABL siRNA to Imatinib-resistant CML cells. These findings suggest that IL3-targeted exosomes are a promising strategy for overcoming pharmacological resistance in CML [166].

Multiple myeloma (MM) ranks as the second most common hematologic malignancy [167], despite significant advancements in patient outcomes with myeloma-targeted and immunomodulatory therapies, remains largely incurable [168]. Currently, bortezomib (BTZ)-driven chemotherapy regimen is the primary frontline regimen for MM [169, 170]. This chemotherapy strategy is associated with notable side effects, including peripheral nervous toxicity, kidney toxicity, and leukocyte reduction [171].

MSCs show significant potential as a cell-based resource for the treatment of numerous illnesses [172]. The clinical effect of MSCs is partly attributed to their generation of EVs [173]. Apoptosis is a regulated process of cell death that generates numerous extracellular vesicles, known as apoptotic vesicles (apoVs), which play a role in metabolic activity and maintaining tissue dynamic equilibrium [174]. In most cases, larger apoptotic EVs are classified as apoptotic bodies (ApoBDs), ranging from 1 to 5 μm in diameter. In contrast, smaller EVs are referred to as apoptotic microvesicles (ApoMVs), with sizes between 100 nm and 1 μm, due to their resemblance to MVs produced by living cells [175, 176]. Recently, vesicles resembling exosomes (less than 150 nm) that are released during apoptosis have also been identified and characterized [177, 178]. ApoVs encompass a range of proteins, nucleic acids, lipids, and organelle structures (181). They have been shown to improve osteopenia by transferring various cellular factors [180], inhibit MM by triggering the Fas-ligand [FasL]/Fas pathway [181], reduce septicemia by modulating neutrophil apoptosis [182], and alleviate type 2 diabetes by promoting hepatic macrophages to adopt an inflammation-suppressing phenotype [183]. Zeyuan Cao et al. demonstrate that apoptotic MSCs are able to enclose pH- sensitive BTZ-loaded polymeric nanoparticles within apoVs, enhancing treatment effectiveness by generating a collaborative anti-MM effect that leverages the benefits of both BTZ and apoVs. BTZ/PC-apoVs significantly increased apoptosis in MM cells in vitro. Compared to treatment through BTZ or apoVs alone, BTZ/PC-apoVs showed a stronger anti-tumor activity [184].

Lymphoma, a complicated hematologic neoplasm, manifests as a widely distributed cancer in the body originating within the lymphohematopoietic system. It is mainly divided into two primary categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Among these, NHL is particularly predominant, making it a common type of lymphatic disorder [185]. While chemotherapy in combination with other cell-toxic agents continues to be the most widely used treatment, traditional chemotherapy agents have constraints such as limited targeting ability, adverse reactions, elevated drug tolerance, and poor targeting precision. These factors contribute to significant adverse reactions in patients [186]. Developing drug delivery systems that can accurately transport remedial compounds directly to tumor cells is crucial. By focusing on targeted delivery, these devices aim to enhance treatment effectiveness as it also reducing damage to normal tissues, thereby reducing side effects and overcoming some of the limitations of conventional chemotherapy [187].

Research suggests that combining nanotechnology with cell membranes and EVs offers a prospective approach to

overcoming immune response challenges. This synergy can improve nanoparticle stability and target specificity, allowing therapeutic agents to reach their intended sites with greater efficiency [188]. Using cell membranes and EVs as carriers in nanomedicine offers significant advantages, including exceptional biological compatibility, biodegradability, and a superior drug-loading performance. These characteristics allow these carriers to escape immune surveillance, providing long-lasting circulation support and effective conveyance of therapeutic agents. Additionally, nanopharmaceuticals derived from cell membranes and their byproducts naturally contain targeting ability, making them especially promising for the research and development of drug transport systems in lymphoma treatment. This approach is gaining attention in current research as a means to improve precision and efficacy in cancer therapies [189].

In lymphoma therapy, research predominantly focuses on exosomes due to their promising therapeutic potential. Exosomes are valued for their capability to carry and convey therapeutic substances directly to target cells, enhancing treatment precision and efficacy in combatting lymphoma [190]. Wang et al. presented a groundbreaking method utilizing exosomes capable of dual targeting both lymph nodes and tumors for enhanced tumor immunotherapy. They harnessed macrophages to create immune-stimulated macrophage-tumor hybrid cells, and the chimeric extracellular vesicles from them have dual-targeting and combined mechanisms to enhance the immune response and immunotherapy outcomes.The study showed that these chimeric exosomes effectively slowed tumor development within multiple animal tumor models, involving lymphoma, outperforming the performance of traditional tumor vaccines and T-cell re-infusion treatments [191]. Accompanying the rapid progress in this field, exosomes have shown tremendous prospect for treating NHL. They offer bright prospects and renewed aspiration for lymphoma patients by enhancing targeted therapy options and improving overall treatment efficacy.

Although lipid nanoparticles and other well-established delivery systems have reached a relatively mature stage, using nanoparticles coated with outer membranes and EVs for lymphoma therapy is still in its initial stages. The commercialization of exosome-based vehicles faces numerous obstacles, including not fully developed preparation techniques, variable requirements, limited repeatability, and constraints in feature analysis methods. Current approaches to validate the success of membrane coating primarily rely on particle dimensions measurements and morphology-related assessments. Protein blotting can confirm the resemblance between the surface components of the delivery system and the originating cell membrane, yet it is absent of the capability to detect possible partial membrane structure damage post-coating. To fully address these issues, a comprehensive clinical evaluation is necessary, focusing on direct and quantitative assessments. Such evaluations would facilitate accurate comparisons with other carriers, such as liposomes, to better understand the risk-benefit profile of exosome-based systems and to refine preparation methods for consistent quality in potential commercial applications [187].

Hematologic tumors, such as leukemia and lymphoma, are associated with complex immune microenvironments where tumor-associated immune cells (e.g., Tregs and MDSCs) and immune checkpoints (e.g., PD-1/PD-L1) play significant roles in immune evasion, potentially diminishing the efficacy of exosome-based therapies [192]. Additionally, the high heterogeneity of these tumors, with different subtypes responding variably to treatment, presents challenges for exosome delivery systems. Exosome stability in the bloodstream is another key concern, as they can easily bind to plasma proteins, forming immune complexes that lead to recognition and clearance by the immune system, ultimately reducing their concentration and effectiveness at tumor sites [193]. To address the challenges of exosome-based therapies in hematologic tumors, several strategies can be applied. Exosomes can be functionalized with immune-modulating agents (e.g., immune checkpoint inhibitors) to overcome immunosuppressive tumor microenvironments. Surface modifications, such as adding tumor-specific ligands or antibodies, can enhance targeting and address tumor heterogeneity. Additionally, coating exosomes with stealth polymers like PEG can prevent immune clearance and prolong circulation time [194].

Nervous system

Glioblastoma (GB) is a lethal cancer with complex treatment due to brain and tumor factors like the Blood-brain barrier (BBB), tumor variety, and identified subpopulations with potential changes and different treatment responses [195–197]. At present, there are only a few treatment choices available for GB apart from surgical removal, radiation therapy, and chemotherapy. Although these approaches have been demonstrated to slightly enhance patient survival, patients, particularly those diagnosed with GB, frequently encounter a recurrence of their illness [198, 199]. Upon disease recurrence, treatment choices become scarcer since additional surgical resections could pose life-threatening risks to the patient, patients might not be eligible for further radiation, and the recurrent tumor might be resistant to chemotherapy [200, 201]. GB tumors are related to neural stem cells and Myc signaling, but effective targeting of Myc in clinical practice is yet to be achieved despite efforts, and there

are various challenges in translating related strategies to clinical settings [202, 203].

Exosomes are a key component of intercellular signaling networks, transporting polypeptides, metabolic products, and nucleic acids between both adjacent and remote cells [204]. A variety of small molecule drugs, chemotherapy agents, and RNAi have been triumphantly incorporated into exosomes and dispatched to target cells in vitro and in experimental preclinical models, where they have shown antineoplastic effectiveness [205]. Exosomes derived from human bone marrow mesenchymal stem/stromal cells (BMSCs) have been created as FDA-approved medication transport carriers, owing to their strong security assessment and limited immunogenic characteristics. These exosomes are presently being evaluated in multiple clinical studies [206, 207]. Amanda R. Haltom et al. utilize engineered MSC-derived exosomes to convey siRNAs targeting Myc and assess their mechanistic effects on tumor progression and survival in mouse models of GB. The study consequences indicate that siRNA targeting the Myc gene, delivered via exosomes derived from human bone marrow mesenchymal stem cells (iExo-Myc), exhibits significant anti-tumor effects against GB. Specifically, iExo-Myc successfully localizes to GB tumors in mice, significantly inhibiting tumor proliferation and angiogenesis. This inhibition results in slower tumor progression and extends the survival of the mice. Transcriptomic analysis revealed that Myc inhibition induces transcriptional changes in tumor cells, suppressing pathways associated with tumor invasion and promoting a transition from a mesenchymal to a proneural phenotype. Further single-cell RNA sequencing showed that iExo-Myc induced a shift in GB cells from a mesenchymal to a proneural state and downregulated genes related to cell proliferation and inflammation . These results confirm the promise of Myc as a therapeutical target for GB and demonstrate that delivering Myc siRNA via exosomes is an effective strategy for extending the survival of GB-bearing mice. This approach not only overcomes the limitations posed by the blood-brain barrier but also provides a new avenue for targeting difficult-to-inhibit oncogenes [208].

The main challenge in applying exosomes for treating neurological tumors lies in overcoming BBB. While exosomes are natural nanoparticles with the potential to cross cell membranes, their ability to penetrate the BBB is limited due to their size, lipid bilayer structure, and surface proteins. The BBB effectively restricts most therapeutic agents, including exosomes, from reaching the brain, which poses a significant obstacle in their use for neurological tumor treatment. Additionally, the unique immune microenvironment and high tumor heterogeneity in the nervous system further complicate exosome-based therapies. These factors necessitate advanced strategies to enhance exosome delivery, such as surface modification, targeting specific receptors, and combining with other delivery systems to improve their efficacy in treating brain tumors [209]. Recent breakthroughs in GB therapy have underscored the transformative potential of exosome-based drug delivery systems in overcoming the challenges posed by the BBB. A pioneering study employed exosomes derived from rat C6 glioma cells to CTX and doxorubicin DOX, leveraging CTX's targeting of EGFR-expressing GB cells. This innovative system not only significantly enhanced drug penetration across the BBB but also improved therapeutic concentrations in brain lesions, effectively inhibiting tumor proliferation and migration. In vivo, this approach extended the survival of glioma-bearing rats by 47% compared to DOX monotherapy, demonstrating its potential as a synergistic treatment strategy [210]. Complementing this, another study utilized exosomes derived from BV2 microglial cells, which exhibit natural BBB-penetration capabilities. These exosomes were functionalized with a redox-responsive oligopeptide (Pep2) to lock drug cargo during circulation, ensuring controlled release within the tumor microenvironment. The Pep2-modified exosomes demonstrated superior drug retention in GB tissue, significant anti-tumor activity, and excellent biocompatibility, with no observed toxicity in other organs. Together, these advancements highlight exosome-based platforms as a promising frontier in GB therapy, offering precise targeting, enhanced drug efficacy, and minimized systemic side effects, thereby paving the way for a new era in brain tumor treatment [211].

Genitourinary system

Breast cancer (BC) still a major health problem, contributing to a considerable number of cancer deaths among women across the globe. Despite advancements in conventional therapies, clinical toxicity and lack of precise targeting continue to hinder effective BC treatment [212, 213]. Nano-therapeutics has introduced exosomes (Exo) as a potential treatment option. These minute vesicles are secreted by multiple cell types, such as tumor cells. Exosomes derived from tumor cells can specifically target tumors, facilitate tissue restoration, and regulate the immune response. Compared to other drug delivery methods, exosomes offer several advantages, including improved bioavailability, greater stability, and reduced off-target cytotoxicity and immunogenicity [214, 215].

BC cells exhibit a heightened reliance on fucose, a sugar essential for their proliferation and division, causing greater dependence on it compared to normal cells. This fucose reliance presents potential avenues for targeted therapeutic interventions. CQDs have appeared as an effective method for specifically targeting and treating a range of cancers, including BC. Fucose-based CQDs

provide benefits such as biodegradability, biocompatibility, aqueous dispersibility, and antioxidant and anticancer properties [216]. Fucose-based Quantum Dots (QDs)can effectively deliver therapeutic agents to BC cells while also demonstrating inherent anticancer properties by generating reactive oxygen species (ROS). Yet, their compatibility for different types of cells, not limited to tumor cells, generates worries about potential interactions with normal cells. Furthermore, the volume variability of QDs influences cellular absorption dynamics: larger QDs may struggle to penetrate cells, while smaller QDs are more likely to enter cells but may pose a risk of cellular damage. Despite these challenges, fucose- conjugated QDs hold promise for targeted drug transport in BC therapy, provided these issues are addressed [217].Dacarbazine (DC) is a chemotherapy prodrug that exerts anticancer effects through metabolic activation in hepatic tissue and covalent linkage to DNA molecules in tumor cells, causing DNA strand cross-linking and apoptosis [218]. While DC has demonstrated effectiveness in cancers such as Hodgkin lymphoma and metastatic melanoma, its functions and treatment promise in BC are not yet fully explored [219]. Its application in BC treatment faces challenges due to limited solubility in water, vulnerability to light-induced degradation, and a brief biological half-life. These restrictions can negatively impact medication delivery, bioavailability, and treatment potency, potentially causing non-specific cytotoxicity to nomal cells and leading to harmful side effects [220].

Pratiksha Tiwari et al. formulated a method for the targeted administration of the chemotherapy drug DC to BC cells utilizing CQDs. To enhance DC's solubility and photostability, it was loaded onto CQDs and subsequently enclosed within exosomes originating from BC cells (Ex-DC@CQDs) for targeted therapy. Exosomes are able to specifically target tumor cells via HSPG receptors and protect the consistency of DC and CQDs throughout delivery [221]. Exosomes accelerate the delivery of DC@CQDs to tumor cells, possess unique proteins adhering to HSPG receptors, initiate membrane invagination, facilitate transport of contents, and enable triggering of DC, aiming to enhance therapeutic efficacy and reduce adverse effects [222]. Therefore, exosomes co-encapsulated with CQDs and DC offer substantial curative benefits against BC simultaneously mitigating many of the dangers related to free DC. Additionally, exosomes inherently contain the capability to pass through biological barriers, allowing them to restore internalized medications that are lost in circulation. To facilitate this, CQDs were first synthesized via microwave techniques [223, 224]. Thereafter, the synthesized CQD was incorporated with DC, and the formulations were adjusted for optimal performance to achieve pharmaceutical specifications with enhanced filling capacity. The resulting formulations underwent extensive characterization through both in-vitro and in-vivo experiments. Overall, these findings suggest that BC cell-derived exosome-coated carbon quantum dots offer promising prospects as a new targeted treatment approach for BC. The exosome-CQD complex demonstrated tremendous potential in cancer therapy through effective targeting mechanisms, improved pharmacokinetics, and enhanced drug efficacy [221].

Ovarian cancer (OC) is the eighth most common and fifth deadliest cancer in women worldwide, with a high incidence and mortality rate [225]. The prognosis of ovarian cancer patients is not optimistic, and the survival rate is merely 47.5% [226]. The present first-line treatment for ovarian cancer comprises a combination of cytoreductive surgery and platinum-based chemotherapy [227]. Targeted therapy, such as anti-VEGF antibodies and PARP inhibitors, can be utilized for certain patients [228]. Nevertheless, over half of the patients will suffer a recurrence within two years, leading to little or no enhancement in the survival rate [229, 230].This underscores a dire demand for the development of novel therapeutic approaches [231].

Epigenetic regulation and m6A modification, along with dysregulation of related regulators like YTHDF1, play crucial roles in tumor onset, progression, and chemotherapy tolerance [232, 233]. In the traditional approaches to treating OC, DTX has emerged over recent decades as a new-generation chemotherapeutic drug. Unlike traditional chemotherapy agents, it does not interfere with gene synthesis in tumor cells or cause DNA damage. Instead, it disrupts the dynamic equilibrium between microtubules and tubulin dimers, affecting cell mitosis, ultimately suppressing cell growth and triggering apoptosis [234]. In spite of the strong anti- cancer effects of DTX, treatment tolerance and tumor relapse have been identified as significant challenges [235]. A potential strategy to address these challenges involves downregulating m^6A modulators, which have demonstrated potential in boosting chemotherapy sensitivity and enhancing tumor inhibition. Rong Du et al. aim to develop a combination therapy for enhanced OC treatment by integrating YTHDF1-targeting epigenetic therapy with DTX-mediate chemotherapy. This approach could involve using siRNA to inhibit YTHDF1 expression. As an emerging programmable gene interference technique, siRNA offers high specificity and flexibility in targeting the diseased human genome [236]. Since m6A modification is prevalent in both eukaryotic messenger and non-coding RNAs, achieving efficient tumor localization and selectiveness is essential for minimizing the systemic toxicity and immunogenic response associated with m^6A reader-related epigenetic therapies [237]. Given the potential to reverse chemotherapy resistance by interfering with YTHDF1,

the combinational therapy strategy is anticipated to yield a synergistic therapeutic effect.

MSC-derived small extracellular vesicles (MsEVs) deliver both the lipid membrane and cytoplasmic components from MSCs, demonstrating a natural tumor-homing effect. This makes them well-suited as drug transport systems for cancer treatment [238, 239]. SEVs are crucial in multiple pathophysiological mechanisms, have excellent transcellular permeability and compatibility, can reduce immunological clearance, deliver various cargo, and be used as co-transport vehicles [31]. Rong Du et al. developed an sEV-derived dual-functional nanodrug platform for the co-transport of siRNA targeting the m^6A reader YTHDF1 and the chemotherapy agent DTX for OC therapy. Both DTX and siYTHDF1 were concurrently enclosed into bone marrow MSC-derived sEVs using electropermeabilization. The resulting codelivery system (MsEV-siYTHDF1-DTX) demonstrated enhanced tumor targeting and improved endo/lysosomal evade of siYTHDF1, enabling powerful restraint of OC by lowering YTHDF1 expression and inhibiting EIF3C protein translation in an m6A-dependent fashion. This epigenetic modulation, together with DTX-induced inhibition of microtubule depolymerization, resulted in markedly enhanced tumor suppression and prolonged survival in mice with tumors. This sEV-derived nanoplatform offers a promising approach for optimized co-transport of siRNA and anticancer drugs directed to tumor locations, providing insights into combinational therapy for OC [240].

Renal cell carcinoma (RCC) is a type of urological cancer that has seen an increase in recent years, constituting approximately 3% of all adult cancers [241, 242]. In 2022, the incidence and mortality rates of RCC were high in both China and the United States [243]. Pathological analysis classifies RCC into different subtypes, with ccRCC being the most common, accounting for about 75% of cases [244]. The incidence of RCC increases with aging and is predominant in males over females. Predominant risk factors for RCC include obesity, hypertension, and smoking. CcRCC, the most common subtype, is related to VHL gene variations and involves other genetic and epigenetic changes, with a specific tumor microenvironment [245].Approximately 70% of RCC patients are initially diagnosed with localized disease and undergo nephrectomy, while about 30% have metastasis at diagnosis or during follow-up [246]. In recent years, treatments for metastatic RCC have advanced significantly through targeted therapies and immune checkpoint inhibitors, with different types and targets [247]. Nevertheless, even in conjunction with targeted therapies and immunological treatment for metastatic RCC, the median survival duration remains around 48 months. Persistent issues such as therapeutic resistance and immune-related adverse events (irAEs) continue to challenge treatment effectiveness and patient outcomes [248].

Exosomes can deliver small molecules to targeted cells or tissues for targeted therapy and improve therapy accuracy and efficacy [26]. Exosomes are crucial for facilitating communication between cells, and leveraging this function can be beneficial in therapies aimed at inhibiting RCC infiltration. For example, Yoshino et al. discovered that miRNA-1 (miR-1) could effectively inhibit RCC proliferation and infiltration. Their study demonstrated that when RCC cells were handled with exosomes originated from miR-1-transfected cells, miR-1 expression increased significantly within these cells. miR-1 expression increased approximately 10 to 40 times compared to the control group. It significantly inhibited the growth, migration, and invasion of 786-o and A498 cells. This finding suggests that using exosomes to deliver miR-1 could be a promising therapeutic approach for RCC [249]. YAO ZHANG et al. develop a novel vaccine for RCC. Exosomes originated from IL-12-anchored renal cancer cells have been found to express the RCC-associated antigen G250 and glycolipid-anchored IL-12 (GPI-IL-12). Remarkably, exosomes containing GPI-IL-12 can notably enhance T cell reproduction, leading to an increased release of IFN-γ. Additionally, exosomes with GPI-IL-12 are capable of inducing antigen-targeted CTLs, which results in notable cytotoxic responses. These findings suggest that exosomes from IL-12-anchored RCC, which contain both GPI-IL-12 and G250, hold potential for future applications in RCC treatment [250]. Furthermore, a different study indicated that circSPIRE1 found in exosomes has the potential to suppress the metastasis of RCC. It was shown to enhance the expression of polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) and KH domain RNA binding protein (QKI). GALNT3 enhances glycosylation and facilitates the membrane positioning of E-cadherin, while QKI establishes a positive feedback loop to increase circSPIRE1 levels. Furthermore, exosomal circSPIRE1 can inhibit both angiogenesis and vascular permeability, further contributing to its anti-metastatic effects in RCC [251].

Exosome-based therapy for urogenital system tumors faces unique challenges, including physiological barriers [such as the urine environment and epithelial barriers], tumor immune evasion, tumor heterogeneity, hypoxic vascular environments, and immune clearance. These challenges necessitate the development of targeted exosome delivery systems, employing strategies such as surface functionalization, targeted delivery, immune-modulating molecule loading, and enhanced exosome stability to overcome these physiological and immune barriers, ultimately improving the therapeutic efficacy of exosomes in treating urogenital system tumors [252].

Dermal system

Malignant melanoma(MM) is the most invasive and fast-proliferating type of skin cancer, responsible for 65% of deaths related to skin tumor [253]. The survival rate at 5 years for individuals diagnosed with metastatic melanoma is under 5% [254]. The Chinese guidelines for melanoma diagnosis and treatment, along with recommendations from the American Society of Clinical Oncology, suggest that only early-stage melanoma is suitable for surgical intervention. For primary or metastatic melanomas that are inoperable, radiotherapy may be considered; however, its impact on survival time is minimal. Furthermore, the overall effectiveness of DC, the FDA-approved chemotherapeutic drug for MM, is limited, with a response rate of only 10–15% [255]. While targeted therapies and monoclonal antibodies have shown some efficacy, their clinical application is limited due to high costs, intolerable adverse effects, and the progression of therapeutic tolerance [256]. There is a pressing need for new and targeted therapeutics for MM, and natural products such as triptolide show promise [257]. Triptolide has been shown to inhibit various types of tumors [258–260], by regulating cell growth, apoptosis, autophagocytosis, and angiogenesis [261].Nevertheless, the therapeutic promise of triptolide is limited due to its poor water solubility, brief half-life, and biological toxicity. Consequently, developing an optimal vehicle for the targeted transport of triptolide to cancer tissues is essential to improve its effectiveness and minimize toxicity [262].

Nanotechnology-mediated transport systems offer improved efficacy, reduced toxic side effects, and a significant potential for drug encapsulation [263]. During recent years, nanotargeted transport systems have been demonstrated to significantly reduce toxicity and extend the circulation time of triptolide, enabling targeted transport of therapeutic agents [264]. However, carriers for delivering triptolide still face challenges, including uncontrolled drug release before reaching the target site, rapid clearance by the mononuclear phagocytic system (MPS) [265], and uncertain biological safety [266]. Luckily, biological materials provide alternative methods as innovative carriers to address these limitations. Yongwei Gu et al. aim to utilize cRGD to develop engineered exosomes, focusing on creating a nanoplatform specifically targeting melanoma [262]. As source cells, MSCs are able to be sourced from nearly all human tissues and possess high proliferative capacity, allowing for large-scale exosome production [267]. Especially, human umbilical cord MSCs (hUCMSCs) have garnered significant focus because of their easy accessibility, minimal ethical concerns, straightforward cultivation, and rapid expansion capabilities [268]. The experiment of Yongwei Gu et al. developed the cRGD-Exo/TP system, explored its mechanisms and efficacy in vitro and in vivo, and confirmed its good biosafety for targeted transport of triptolide to melanoma [262].

Skin tumors (such as melanoma, basal cell carcinoma, and squamous cell carcinoma) present a range of unique challenges that impact the application of exosomes in their treatment. The skin is a distinct organ with unique physiological structures and an immune microenvironment, all of which play a crucial role in the design and effectiveness of exosome-based delivery systems [269]. The outermost layer of the skin, the stratum corneum, has a strong barrier function that prevents external substances, including exosomes, from entering the body. This barrier presents one of the biggest challenges in skin treatment. Researchers have proposed methods to enhance the permeability of exosomes, such as using nanotechnology or local application strategies, including surface modifications, liposomes, or microneedle technologies, to improve exosome delivery efficiency in the skin [270]. Another challenge in treating cutaneous tumors is the effective delivery of exosomes to tumor sites. Unlike internal tumors, cutaneous tumors are often more localized, allowing for treatment through topical application and avoiding systemic side effects. However, ensuring that exosomes specifically target the tumor cells remains a challenge. To improve delivery efficiency, exosome surfaces can be modified with tumor-specific targeting molecules, such as anti-BRAF antibodies for melanoma cells, to ensure precise localization and penetration of the tumor tissue [271].

Motor system

Osteosarcoma is the most common malignant tumor that originates in bone tissue, occurring most frequently in children and adolescents [272]. Currently, the standard treatment for osteosarcoma is surgical resection combined with neoadjuvant chemotherapy. Unfortunately, the five-year survival rate for osteosarcoma patients stays at only 60–70% [273, 274]. Additionally, the recurrence rate for osteosarcoma patients remains high even after treatment [275]. One factor contributing to this issue is that the chemotherapy agents utilized for osteosarcoma are not only non-specific but also lack effectiveness, frequently leading to considerable side effects unrelated to the target. Consequently, there is a pressing requirement to create novel targeted therapies with improved tumor-eradicating effectiveness and reduced adverse effects to enhance the survival of osteosarcoma patients.

Nanotechnology systems offer intrinsic benefits as drug transport systems, including prolonged circulation time, small size, and the ability to accumulate within tumors. Li et al. treated late-stage osteosarcoma using apatinib enclosed in hydrophobic poly[ester amide] nanoparticles, which notably inhibited tumor proliferation with

minimal adverse effects [276]. During recent decades, exosomes have emerged as a potential method for delivering chemotherapeutic agents in tumor treatment [277]. However, obtaining highly purified exosomes remains a significant challenge and a complex issue with current technology [278]. In particular, the limited quantity of naturally secreted exosomes poses a challenge for large-scale production [279]. Furthermore, the medication transport efficiency of exosomes as vehicles remains an unresolved issue [280].

Exosome mimetics (Ems) as drug delivery vehicles provide numerous benefits compared to current synthetic systems. To start with, EMs inherently target their source tissues. For the study, Jinkui Wang et al. chose EMs originated from bone marrow mesenchymal stem cells (BMSCs) to target osteosarcoma Second, the phospholipid bilayer of EMs can merge with cell membranes, facilitating the internalization of enclosed drugs. Third, the small size of EMs enhances their ability to extravasate through neoplastic blood vessels and diffuse into tumor tissues. Doxorubicin, a primary chemotherapeutic agent for osteosarcoma, has its clinical dosage significantly restricted due to high toxicity [281]. The research focused on the development of EMs derived from BMSCs for delivering doxorubicin in osteosarcoma therapy. Using sequential extrusion, they produced EMs and enclosed doxorubicin to create EM-Dox. By harnessing the natural tumor-homing ability of BMSC-derived EMs, they targeted osteosarcoma with EM-Dox to treat in situ xenografts. In vitro studies confirmed efficient uptake of EM-Dox by osteosarcoma cells and demonstrated higher cytotoxicity against these cells compared to free doxorubicin. In vivo studies showed that EM-Dox had a longer circulation time and higher accumulation in tumor tissues compared to other carriers, supporting its enhanced targeting capabilities. The findings suggest that EM-Dox could serve as a promising approach to improve osteosarcoma therapy by enhancing drug delivery specificity and minimizing off-target toxicity [282].

Musculoskeletal tumors, such as bone and muscle cancers, present unique challenges, including mineralization barriers in bone tissue, high metabolic rates in muscle, hypoxic and acidic microenvironments, and immune evasion mechanisms [283]. To address these obstacles, exosome delivery systems require multiple strategies. Surface functionalization and targeted delivery—such as modifying exosome surfaces with tumor-specific receptors or antibodies—can enhance exosome recognition and penetration into targeted tumor cells. Additionally, to overcome the hypoxic and acidic conditions, exosome stability and resilience can be improved by encapsulating them in materials like polyethylene glycol or nanoparticles, thereby increasing accumulation at tumor sites [284]. Immune modulation is another crucial strategy; exosomes can carry immune checkpoint inhibitors or immune-boosting molecules to reverse immune evasion and amplify immune responses. Furthermore, given the tumor heterogeneity, designing exosomes with multi-targeting capabilities enables personalized treatment approaches for different tumor subtypes. These combined strategies help overcome the physiological and immune barriers in musculoskeletal tumors, improving the therapeutic efficacy of exosome-based treatments [285].

Challenges and limitations

Despite the significant potential of exosome therapies in cancer treatment (Table 3), several challenges remain in their practical application, necessitating further research and solutions.

Production and scalability

The production of exosomes on a large scale with uniform quality poses considerable challenges related to technical feasibility and cost-effectiveness. Exosomes are complex biological particles, and their production involves intricate cellular secretion mechanisms. Ensuring consistency in the functionality and characteristics of exosomes at scale requires overcoming numerous technical hurdles, such as efficient collection, purification, and storage, while maintaining their biological similarity to naturally secreted exosomes. Furthermore, the production process is often complex and resource-intensive, making cost reduction another major obstacle [286]. Developing scalable manufacturing methods for exosome production remains a critical issue in the development of exosome-induced treatment. The complexity involved in isolating and purifying exosomes, combined with the necessity of customizing them for specific therapeutic applications, significantly amplifies cost of production. Exosomes are derived from intricate cellular processes, and obtaining them in large quantities while maintaining their functional integrity is technically challenging. Furthermore, different therapeutic uses may require specific modifications or customizations of exosomes, adding another layer of complexity to the manufacturing process. This not only increases the difficulty but also inflates the overall cost of production. Therefore, developing cost-effective and scalable production methods is essential for advancing the clinical application of exosome-based therapies [6].

Regulatory and safety issues

As an emerging biological therapy, the regulatory framework for exosomes is not yet clear. Regulatory agencies in different countries and regions have varying definitions and classifications for exosomes, which can complicate approval processes. In treating liver and colorectal

Table 3 Application of Exosomes in different Cancer cell therapies

Cancer Type	Application	Key findings	Reference
Lung Cancer	FA-ExoPAC	Improved drug delivery efficiency and significantly reduced toxicity	[74]
Gastric cancer	Exosome-mediated delivery of miR-21 inhibitors	Stronger inhibitory effects and reduced cytotoxicity	[105]
	DC-derived exosome vaccines	Enhanced the T-cell immune response and tumor rejection	[107]
	ExoDOX	Reduced the cardiotoxicity	[119]
	Exosomal rhTRAIL	Effectively induced apoptosis in tumor cells and no significant toxicity to normal cells	[120]
Liver cancer	Exosomal miR-122	Enhance the chemosensitivity of HCC	[123]
	Exosomal miR-335-5P Exosomal miR-320a	Effectively inhibited HCC proliferation and metastasis	[125, 126]
	A novel HCC treatment vaccine	Enhancing the cytotoxic response of NK cells	[132]
Pancreatic cancer	dtEVs	Effectively suppressed large solid PDAC	[141]
Colorectal cancer	Target-Her2-LAMP2-GFP, THLG-Exo/5-FU/miR-21i	Effectively reversed drug resistance in colorectal cancer cells	[148]
Chronic Myelogenous Leukemia	Modified exosomes containing IL3-Lamp2B, loaded with Imatinib	Reduced tumor size	[166]
Multiple myeloma	BTZ/PC-apoVs	Significantly increased apoptosis in MM cells in vitro and a stronger anti-tumor activity	[184]
Lymphoma	Dual-targeting exosomes	Effectively slowed tumor progression across various animal tumor models, including lymphoma, surpassing the performance of traditional tumor vaccines and T-cell reinfusion therapies	[191]
Glioblastoma	iExo-Myc	Significantly inhibited tumor proliferation and angiogenesis	[208]
Breast cancer	Ex-DC@CQDs	Enhanced tumor targeting and therapeutic efficacy	[221]
Ovarian cancer	MsEV-siYTHDF1-DTX	Significantly improved tumor inhibition and extended survival in tumor-bearing mice	[240]
	Exosomes to deliver miR-1	Suppressed RCC growth and invasion	[249]
Renal cell carcinoma	Exosomes containing GPI-IL-12	Resulted in notable cytotoxic effects	[250]
	Exosomal circSPIRE1	Suppressed both angiogenesis and vessel permeability	[251]
Malignant melanoma	cRGD-Exo/TP	Prolonged circulation time, higher tumor accumulation, and better targeting compared to non-targeted systems	[262]
Osteosarcoma	EM-Dox	Enhanced drug delivery specificity and minimized off-target toxicity	[282]

cancers, regulatory uncertainties may delay clinical trial progress and market promotion. Exosomes may induce immune reactions or unintended biological effects, such as promoting tumor invasion and metastasis9. Studies have shown that tumor cell-derived exosomes can carry oncogenic substances that affect normal cell functions10. Therefore, it is crucial to fully evaluate the safety of exosomes in preclinical studies to ensure patient safety [287].

Clinical translation

Although significant progress has been made in the laboratory research of exosomes, their clinical application remains in its infancy. Currently, only a limited number of clinical trials are investigating the efficacy and safety of exosome-based therapies. The absence of large-scale, randomized controlled trials (RCTs) is a major factor impeding the broader adoption of exosome therapies in clinical practice. In cancers such as prostate and lung cancer, the ongoing clinical trials are still in early stages, and the efficacy, safety, and overall applicability of these therapies need further validation. Key challenges include identifying the optimal dosage, administration route, and determining biomarkers to predict response to exosome therapy. Moreover, the long-term efficacy and potential side effects have yet to be fully understood, which is crucial for establishing standardized treatment protocols. Overcoming these hurdles will require comprehensive, well-designed clinical studies that evaluate not only the immediate therapeutic benefits but also the potential risks associated with long-term use. Systematic clinical research is essential to build a strong foundation for integrating exosome-based therapies into standard cancer treatment paradigms [288].

Future outlook

Emerging trends

Recent advances in the study of exosomes have demonstrated their significant potential in the fields of diagnosis, therapy, and prevention across a variety of diseases. In diagnostics, exosomes are emerging as valuable non-invasive biomarkers for early detection and monitoring of diseases such as cancer, cardiovascular conditions, and neurodegenerative disorders. Their ability to carry disease-specific proteins, RNA, and other molecular

signatures has led to the development of liquid biopsy techniques, offering a less invasive and more accessible method for clinical screening and disease progression tracking [289]. In therapy, exosomes have shown promise as natural delivery vehicles due to their biocompatibility, low immunogenicity, and ability to cross biological barriers. Recent studies have successfully utilized exosomes to deliver therapeutic agents, including small molecules, RNA therapeutics, and anti-cancer drugs, particularly in the treatment of cancers. Their ability to target specific cells or tissues enhances the precision of treatments, reducing off-target effects and drug resistance [290]. In the realm of prevention, exosomes are being explored for their role in immunomodulation. They have the potential to stimulate immune responses or regulate immune functions, which is particularly relevant in the context of vaccines and immune-based therapies. For instance, exosome-based vaccines are being investigated for their ability to present antigens to immune cells, potentially enhancing the efficacy of cancer immunotherapy and infectious disease prevention [291].

Overall, the latest progress in exosome research is driving their application toward becoming pivotal tools in personalized medicine, with significant implications for diagnostics, targeted therapeutics, and preventative healthcare strategies.

Long-term outlook for exosome-based cancer therapy

As research on exosomes advances, they are poised to play an increasingly significant role in cancer treatment, driven by their unique biological properties and versatility. Exosomes, as natural carriers of biomolecules, offer several advantages over traditional therapies due to their ability to selectively target cells, deliver diverse therapeutic payloads, and modulate the tumor microenvironment. The following are speculations on how exosomes could shape future cancer therapies: With the rise of personalized medicine, exosomes could be engineered to deliver tailored therapeutics based on the specific molecular and genetic profile of an individual's tumor. This customization would enable highly targeted treatments with fewer side effects and increased efficacy. By isolating exosomes from a patient's own cells, researchers can further reduce the risk of immune rejection, making exosome-based therapies an attractive option for personalized cancer treatment [292]. In the future, exosomes could become the primary vehicles for drug delivery, overcoming the limitations of synthetic nanoparticles. Due to their natural origin, exosomes are biocompatible and can evade the immune system, allowing for the delivery of a wider range of therapeutics, including small molecules, siRNAs, and CRISPR-Cas9 gene editing tools. This would be particularly useful for cancers that are difficult to treat with conventional methods, such as GBs, where exosomes could cross the blood-brain barrier more effectively than traditional therapies [41].Exosomes have the potential to revolutionize cancer immunotherapy by serving as vehicles for immune checkpoint inhibitors or other immune-modulating agents. Additionally, they could be used to develop novel cancer vaccines. Tumor-derived exosomes that carry tumor-associated antigens could be engineered to stimulate an immune response, training the patient's immune system to recognize and destroy cancer cells. This exosome-based vaccine approach could complement existing immunotherapies like CAR-T cell therapy and checkpoint inhibitors [293, 294]. One of the most promising future roles for exosomes in cancer treatment is their ability to modulate the TME. By reprogramming the TME to be less supportive of tumor growth and metastasis, exosome-based therapies could help to suppress cancer progression. Exosomes could carry therapeutic molecules that inhibit angiogenesis, block cancer cell communication, or induce immune cell infiltration into the tumor, creating a hostile environment for cancer cells to thrive [295].

Conclusion

The research and development of exosome-based drug delivery systems have ushered in a transformative approach to cancer therapy, offering unprecedented potential for personalized medicine, enhanced therapeutic efficacy, and the ability to overcome some of the longstanding challenges of conventional treatments. Exosomes' unique properties, such as high biocompatibility, ability to deliver a wide range of therapeutic agents, and natural targeting capabilities, make them an ideal tool in the fight against cancer. Studies have demonstrated that exosomes can be engineered to deliver chemotherapeutic agents, gene therapies, and immunomodulators with a high degree of specificity to cancer cells, minimizing damage to healthy tissues and reducing systemic toxicity. These innovations not only improve patient outcomes but also present a compelling case for further exploration of exosome-mediated therapies in clinical settings.

Despite these advances, significant challenges remain in scaling the production of exosome-based therapies, ensuring quality control, and addressing safety and regulatory concerns. Current limitations in the large-scale manufacturing of exosomes, as well as the complexities involved in purifying and characterizing these vesicles, hinder their widespread clinical application. Moreover, while preclinical studies and early-phase clinical trials have shown promise, translating these findings into widely accessible treatments requires overcoming significant scientific and regulatory hurdles. Addressing these challenges is critical for the successful integration of exosome-based therapies into mainstream cancer treatment protocols.

Moving forward, research should focus on optimizing exosome biogenesis, cargo loading, and targeting mechanisms to enhance therapeutic delivery while minimizing side effects. Additionally, advancements in synthetic exosomes and hybrid systems that combine natural exosome properties with engineered features are poised to further revolutionize cancer therapy. The future of exosome-based drug delivery looks promising, with potential applications not only in cancer but also in a range of other diseases, marking a new frontier in the precision medicine landscape.

Abbreviations

siRNA	Small interfering RNA
EVs	Extracellular vesicles
MVBs	Multivesicular bodies
ILVs	Intraluminal vesicles
ESCRT	Endosomal sorting complexes required for transport
R-EXO	Recombinant exosomes
TMZ	Temozolomide
DHT	Dihydrotanshinone
DLS	Dynamic light scattering
TEM	Transmission electron microscopy
NTA	Nanoparticle tracking analysis
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
EGFR	Epidermal growth factor receptor
PD-1	Programmed death protein 1
ExoPAC	Exosome-loaded paclitaxel
DDR	DNA damage response
ROS	Reactive oxygen species
DCs	Dendritic cells
TAA	Tumor-associated antigen
GC	Gastric cancer
H. pylori	Helicobacter pylori
MSCs	Mesenchymal stem cells
CTLs	Cytotoxic T lymphocytes
TDEs	Tumor-derived exosomes
HCC	Hepatocellular carcinoma
EMT	Epithelial-mesenchymal transition
MDR	Mechanisms behind multidrug resistance
AMSCs	Adipose tissue-derived mesenchymal stem cells
HSPs	Heat shock proteins
PDAC	Pancreatic ductal adenocarcinoma
LNPs	Liposomal nanoparticles
dtEVs	Dual-targeted therapeutic extracellular vesicles
hmAb	Humanized monoclonal antibodies
MEF	Mouse embryonic fibroblast
hBMSCs	Human bone marrow stem cells
GEM	Gemcitabine
PDX	Patient-derived xenograft
OXA	Oxaliplatin
ICD	Immunogenic cell death
CRC	Colorectal cancer
CML	Chronic Myelogenous Leukemia
TKIs	Tyrosine kinase inhibitors
AML	Acute myeloid leukemia
MM	Multiple myeloma
apoVs	Apoptotic vesicles
NHL	Non-Hodgkin's lymphoma
GB	Glioblastoma
BBB	Blood-brain barrier
BC	Breast cancer
CQDs	Carbon Quantum Dots
OC	Ovarian cancer
EIF3C	Eukaryotic translation initiation factor 3 subunit C
MsEVs	MSC-derived small extracellular vesicles
RCC	Renal cell carcinoma
ccRCC	Clear cell renal cell carcinoma
TT	Targeted therapies
ICIs	Immune checkpoint inhibitors
VEGF	Vascular endothelial growth factor
CTLA-4	Cytotoxic T-lymphocyte associated protein-4
MM	Malignant melanoma

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Jiale Li wrote the manuscript and drew the figures and tables. Zigui Chen and Jiachong Wang provided the conceptualization and review of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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