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Review paper

Extracellular vesicles in anti-tumor drug resistance: Mechanisms and therapeutic prospects

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ABSTRACT

Drug resistance presents a significant challenge to achieving positive clinical outcomes in anti-tumor therapy. Prior research has illuminated reasons behind drug resistance, including increased drug efflux, alterations in drug targets, and abnormal activation of oncogenic pathways. However, there's a need for deeper investigation into the impact of drug-resistant cells on parental tumor cells and intricate crosstalk between tumor cells and the malignant tumor microenvironment (TME). Recent studies on extracellular vesicles (EVs) have provided valuable insights. EVs are membrane-bound particles secreted by all cells, mediating cell-to-cell communication. They contain functional cargoes like DNA, RNA, lipids, proteins, and metabolites from mother cells, delivered to other cells. Notably, EVs are increasingly recognized as regulators in the resistance to anti-cancer drugs. This review aims to summarize the mechanisms of EV-mediated anti-tumor drug resistance, covering therapeutic approaches like chemotherapy, targeted therapy, immunotherapy and even radiotherapy. Detecting EV-based biomarkers to predict drug resistance assists in bypassing anti-tumor drug resistance. Additionally, targeted inhibition of EV biogenesis and secretion emerges as a promising approach to counter drug resistance. We highlight the importance of conducting in-depth mechanistic research on EVs, their cargoes, and functional approaches specifically focusing on EV subpopulations. These efforts will significantly advance the development of strategies to overcome drug resistance in anti-tumor therapy.

1. Introduction

Cancer stands as a notable contributor to global morbidity and mortality, with an estimated 19.3 million new cases and nearly 10 million fatalities attributed to cancer in 2020 according to GLOBOCAN 2020 [1]. Extensive research has delved into pharmacological therapy to combat tumors, demonstrating remarkable therapeutic efficacy in specific cancer patients. However, the persistence of drug resistance presents a formidable hurdle to achieving favorable treatment outcomes. Hence, a profound exploration into the underlying mechanisms of anti-tumor drug resistance becomes imperative. While earlier investigations were primarily concentrated on intracellular modifications that foster drug resistance, such as abnormal activation of anti-apoptotic pathways and modifications in drug metabolism, recent research has hinted at the influence of tumor microenvironment (TME) on drug resistance [2]. Contemporary times have seen the elucidation of extracellular vesicles (EVs) yield novel insights into the intricate mechanisms governing anti-tumor drug resistance.

EVs are membrane-bound particles that are secreted by all living cells. EVs play a crucial role in intercellular communication by encapsulating various cargo, such as DNA, RNA, lipids, metabolites,

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cytosolic and surface proteins. The delivery of these cargo molecules by EVs has a significant impact on the behavior and phenotype of recipient cells [3–7]. Notably, EVs, particularly those originating from tumor cells, have demonstrated a role in promoting tumor progression, metastasis, and the establishment of an immunosuppressive TME [8,9]. Aberrant secretion and cargo packaging of EVs have been documented in drug-resistant tumor cells [9–14], closely linked to an unfavorable prognosis in anti-tumor therapy. Mechanisms of transferring drug resistance from drug-resistant tumor cells to parental counterparts encompass an array of pathways, including enhanced drug efflux, dysregulation of apoptosis, initiation of autophagy, and other interconnected processes. Furthermore, EV-mediated interaction between malignant parenchymal cells and the TME can trigger TME reprogramming and amplify drug resistance by causing T cell dysfunction and more. Given the pivotal role of EVs within the context of anti-tumor drug resistance, the evolution of EV-centered applications and therapeutics holds the potential to overcome drug resistance barriers within anti-tumor therapy. Serving as vital carriers for essential molecules from parent cells, EVs have been extensively explored as biomarkers in liquid biopsy, furnishing valuable prognostic insights and drug resistance indicators. Moreover, inhibition of EV biogenesis and secretion emerges as a promising approach to counteract the passive influence mediated by EVs.

In this review, we have summarized the mechanisms of EV-mediated drug resistance in chemotherapy, targeted therapy, immunotherapy and radiotherapy. Additionally, we have outlined extant strategies rooted in EVs to tackle anti-tumor drug resistance, including EV-based biomarkers for drug resistance prediction and targeted EV inhibition. More importantly, we offer forward-looking perspectives on EVs and drug resistance to anti-tumor therapy, aspiring to pave the way for future research on anti-tumor drug resistance from the perspective of EVs.

2. The classification and biogenesis of EVs

Based on the way of the biogenesis, EVs can be classified into ectosomes and exosomes. Ectosomes, ranging in size from 50 to 1,000 nm, form through outward budding on the plasma membrane. In contrast, exosomes are generated by inward budding within the endosomal pathway, typically measuring around 40–150 nm in diameter (average ~100 nm) [7,9]. For exosomes, the process begins with early endosomes (EE) budding inwardly from the plasma membrane. The endosomal sorting complex required for transport (ESCRT) machinery is recruited, facilitating cargo clustering, membrane bending, and scission, resulting in intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). ILVs can also form via an ESCRT-independent process mediated by Neutral sphingomyelinase 2 (nSMase2). Subsequently, MVBs are transported to the plasma membrane, assisted by Rab GTPases like Rab27, leading to EV release upon fusion with the plasma membrane. Additionally, MVBs can undergo degradation through a lysosome-dependent pathway [8,15] (Fig. 1). These mechanisms underlying EV biogenesis and secretion are shared by all living cells. However, the existing knowledge regarding the differential secretion mechanisms of EV subpopulations derived from different cell sources is still limited. The discovery of regulatory mechanisms and regulators involved in the secretion of EV subpopulations will greatly facilitate the exploration of new therapeutic targets.

3. EV-mediated regulations on recipient cells

EVs are widely present in the communication of various cells. The diversity of effects exerted by EVs on recipient cells has been proved by numerous studies [16]. EVs from different cell sources exert different effects on various recipient cells, driven by variations in the cargoes carried by the EVs and the modes of interaction with recipient cells [17]. The ways in which EVs interact with recipient cells include membrane fusion, endocytosis, phagocytosis, and other mechanisms [18], which ultimately modifies the biological behaviour of recipient cells. For instance, EVs from activated hepatic stellate cells (HSCs) induce a proinflammatory phenotype in Kupffer cells (KCs) by acting Toll-like receptor 4 (TLR4), which leads to liver fibrosis [19]. Comparatively, endothelial cell-derived EVs suppress the activation of monocytes by nuclear factor kappa B (NF-κB) signaling inhibition to diminish the proinflammatory response [20]. These indicated that EVs play a dual role in the regulation of inflammation. Indeed, the role of EVs extends far beyond this. Another study reports that tubular epithelial cell-derived EVs induced by albuminuria triggers glycolysis in renal macrophages by stabilizing hypoxia-inducible factor 1-alpha (HIF-1α) [21]. Moreover, natural killer (NK) cell-derived EVs carrying multiple killing proteins exert a cytotoxic effect on tumor cells by employing caspase-dependent and caspase-independent cascade, as well as causing endoplasmic reticulum stress [22]. Notably, by modulating cellular phenotypes, EVs thereby exert regulatory influences on tissues and even organs. Extensive studies have demonstrated the involvement of EVs in crucial biological processes such as angiogenesis [23], wound healing [24], and nerve and bone regeneration [25,26].

Nowadays, gradually increased researches are focusing on EVs in cancer. Malignant cells generally exhibit higher level of EV secretion compared to normal cells, which are considered as “bad guys” in TME. By transferring oncogenic molecules to tumor cells, EVs endow recipient cells with more malignant characteristics and lead to cancer progression. EV-mediated delivery of S100A10 increases the expression of epidermal growth factor receptor (EGFR), induces AKT and extracellular signal-regulated kinase (ERK) signaling, and enhances stemness and metastasis in hepatocellular carcinoma (HCC) cells [27]. Moreover, EVs can “educate” cells in TME to acquire an immunosuppressive phenotype and ultimately form a tumor-promoting TME. Endothelial EVs enriched in miR-142-5p, miR-183-5p and miR-222-3p are reported to induce M2 polarization of macrophage by targeting phosphatase and tensin homolog (PTEN), which aids in tumor progression [28]. Furthermore, EVs hold the potential to modulate the tumor cells and reprogram TME, leading to tumor drug resistance, through oncogenic delivery and ligand binding (Fig. 2).

4. Mechanisms of EV-induced drug resistance

4.1. Resistance to chemotherapy and targeted therapy

Chemotherapy is a widely employed systemic anti-tumor therapy that effectively kills tumor cels by targeting proliferating cells with chemotherapeutic drugs. Meanwhile, targeted therapy drugs, which have emerged in recent years, specifically inhibit the growth of tumors by targeting identified molecular factors. These therapies offer a higher level of selectivity and reduced toxicity compared to chemotherapy. However, the efficacy of both drug classes is impeded by the presence of drug resistance in tumors (Table S1) [29–51]. Research indicates that EVs also contribute to the development of resistance in both chemotherapy and targeted therapy. Since the mechanisms of drug resistance in both chemotherapy and targeted therapy partially overlap, we are currently discussing the EV-mediated drug resistance in these two therapies collectively (Fig. 3).

4.1.1. Dysregulation of apoptosis

Tumor cells that acquire resistance to pharmacological treatments frequently display inhibited apoptosis, stemming from the

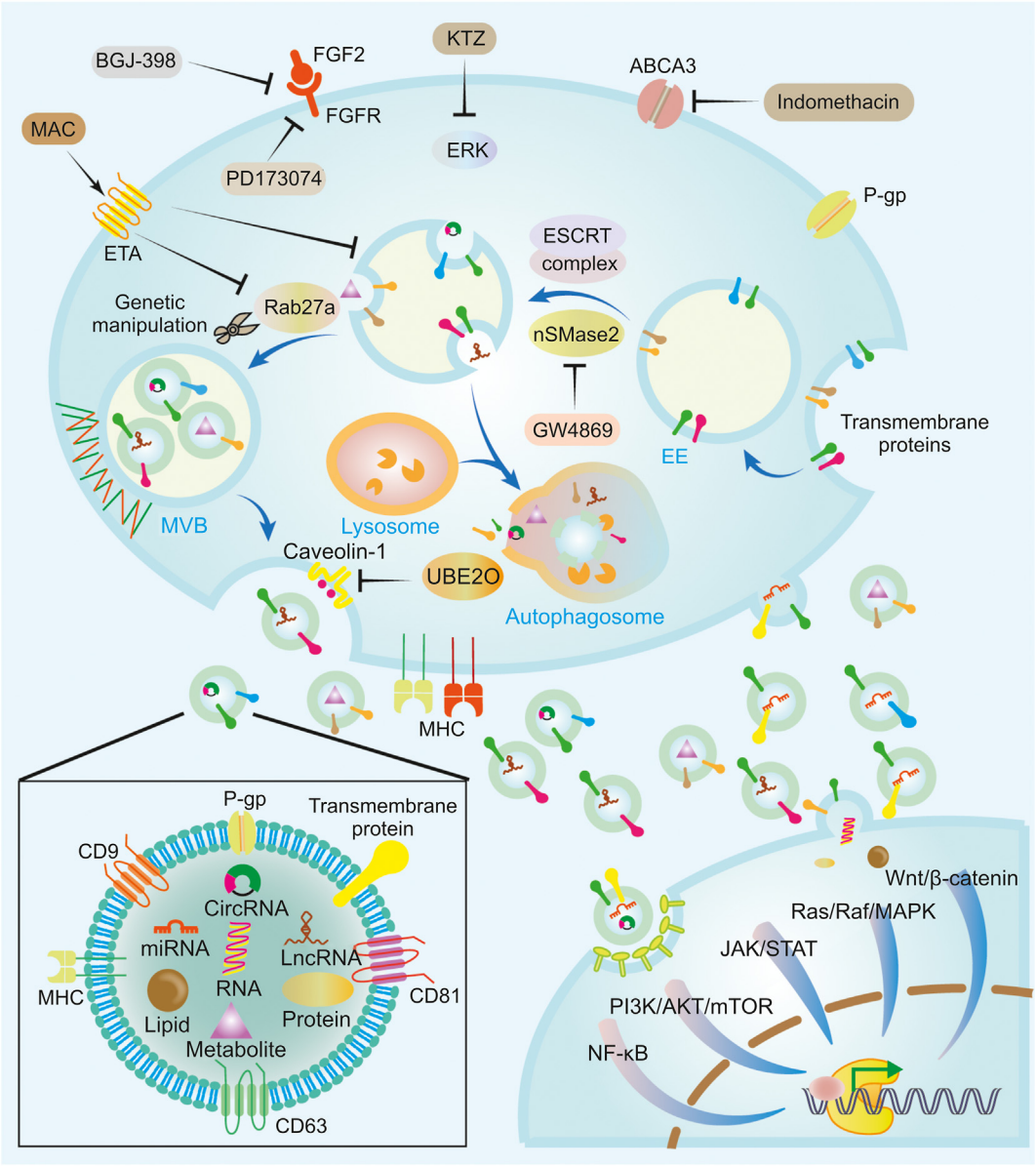

Fig. 1. The biogenesis, secretion, uptake, and inhibition of extracellular vesicles (EVs). EVs are membrane-bound particles with various cargoes. EVs are generated in two manners. One is by outward budding of the plasma membrane. While the other undergoes early endosome (EE) formation via inwardly budded plasma membrane, formation of intraluminal vesicles in multivesicular bodies (MVBs), MVB docking to the plasma membrane, MVB fusion with the plasma membrane, and EV secretion. MVBs can also be degraded in a lysosome-dependent manner. A vast array of cargoes is loaded onto EVs and subsequently secreted in an EV-dependent manner. Several molecules have been studied as inhibitors of EV biogenesis and secretion. Once transported within the extracellular space, EVs can be taken up by recipient cells, thereby modulating cellular signals within recipient cells. MAC: macitentan; ETA: endothelin receptor A; MVB: multivesicular body; UBE2O: ubiquitin-conjugating enzyme E2O; MHC: major histocompatibility complex; FGF2: fibroblast growth factor 2; FGFR: fibroblast growth factor receptor; KTZ: ketoconazole; ERK: extracellular signal-regulated kinase; ESCRT: the endosomal sorting complex required for transport; nSMase2: neutral sphingomyelinase 2; EE: early endosome; P-gp: P-glycoprotein; ABCA3: ATP-binding cassette A3; PI3K: phosphatidylinositol 3-kinase; mTOR: mammalian target of rapamycin; JAK: Janus kinase; STAT: signal transducer and activator of transcription; Raf: rapidly accelerated fibrosarcoma kinase; MAPK: mitogen-activated protein kinase.

activation of pro-survival oncogenic pathways or the deactivation of apoptotic pathways. EVs, engaged in cell-to-cell communication, can interfere with apoptosis in pharmacologically stressed tumor cells through ligand-receptor interactions or by delivering oncogenic cargoes. This interference can ultimately foster chemoresistance.

Among the highly activated pathways in tumor cells, the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway looms prominently. Its regulation is adversely affected by the tumor suppressor PTEN. Aberrant PI3K/AKT pathway activation fuels tumor survival, progression, metabolic changes, and drug resistance [52,53]. For instance, EV miR-1238 generated by temozolomide (TMZ)-resistant glioblastoma (GBM) cells has been found to transfer chemoresistance to other GBM cells. This transfer is achieved by targeting caveolin-1 (CAV-1), a structural protein present in caveolae within lipid rafts, which is known to regulate various cellular signaling processes involved in cell growth and migration. Subsequently, the activation of the EGFR/PI3K/AKT/mTOR pathway is stimulated, further contributing to chemoresistance in GBM cells [54–57]. Beyond direct PI3K/AKT pathway activation, PTEN inhibition indirectly stimulates this oncogenic route, culminating in chemoresistance.

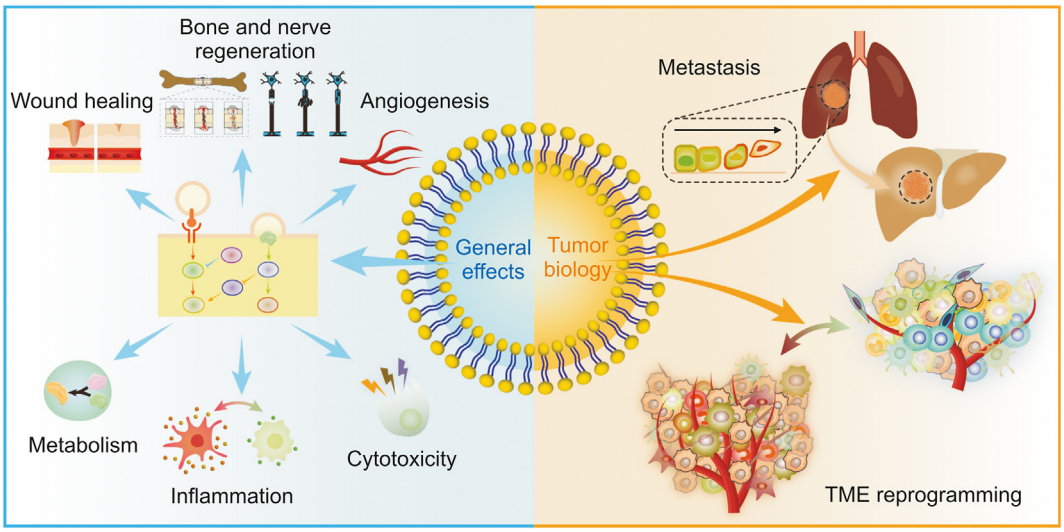

Fig. 2. Schematic diagram summarizing cells receiving the information of extracellular vesicles (EVs). EVs are proficient in transmitting diverse information to target cells, regulating cellular signals via cargo delivery and interactions with ligand-receptor pairs. Through their interactions with recipient cells, EVs hold the potential to reprogram cellular metabolisms, regulate inflammatory phenotypes, and even exhibit cytotoxic effects. Furthermore, modulating cellular phenotypes, EVs possess the ability to induce profound changes at the tissue and organ levels, including processes such as wound healing, angiogenesis, and the bone and nerve regeneration. Within the realm of tumor biology, EVs play a pivotal role in the tumor metastasis through the delivery of oncogenic cargoes. Additionally, EVs are capable of orchestrating the tumor microenvironment (TME) reprogramming, thus creating a conducive milieu for tumor promotion. TME: tumor microenvironment.

M2-polarized macrophage-released EVs harbor abundant LncRNA CRNDE, inducing cisplatin resistance in gastric carcinoma (GC) through facilitating neural precursor cell expressed developmentally down-regulated 4-1 (NEDD4-1)-mediated PTEN ubiquitination [58]. Similarly, $CD63^{+}$ cancer-associated fibroblast (CAF)-derived miR-22-rich EVs hinder PTEN expression, hyper-activating PI3K/AKT signaling in estrogen receptor (ER) positive breast cancer (BC) cells, thus fostering tamoxifen resistance [59]. To sum up, the capability of EVs to exploit the PI3K/AKT pathway engenders chemoresistance in cancer.

Apart from pro-survival signaling activation, irregular apoptotic signaling also figures into chemoresistance. The apoptotic caspase family, instrumental in cell apoptosis, hinges on initiator caspases (caspase-2, 8, 9, 10) detecting upstream signals and orchestrating the activation of effector caspases (caspase-3, 6, 7), thereby inducing apoptosis [60] and eradicating malignant cells. Furthermore, stress-related caspase-12 plays an important role in stretch-induced apoptosis that is associated by endoplasmic reticulum stress by activating caspase-3 [61]. Caspase family impediments hinder apoptosis. Illustratively, EV miR-501 secreted by doxorubicin-resistant GC cells drives chemoresistance in recipient GC cells by suppressing BH3-like motif containing, cell death inducer (BLID), inducing apoptosis resistance via caspase-3/9 inactivation, and augmenting tumor malignancy through AKT phosphorylation [62]. Additionally, EV miR-769-5p inhibits the downstream caspase pathway by targeting caspase-9 and promotes p53 ubiquitination degradation via the ring finger protein (RNF)/neural precursor cell expressed developmentally down-regulated 4-like (NEDD4L)/p53 axis, ultimately impeding cisplatin-triggered GC cell apoptosis [63]. Notably, apoptotic caspases hold the potential to trigger drug resistance via multiple mechanisms. Huang et al. [64] have confirmed that activated caspase-3, through its regulation on downstream factor prostaglandin E2 (PGE2), effectively stimulated the growth of surviving tumor cells. Meanwhile, lipid mediators such as prostaglandins are found in EV-mediated communications and exert an influence on TME [65,66]. This suggests that EVs may be involved in the caspase-3/PGE2 axis, which could lead to drug resistance. If so, non-steroidal anti-inflammatory drugs such as indomethacin, which targets Cox2/PGE2, may serve as a therapeutic intervention to disrupt this undesirable process. Moreover, miR-21 is transferred from cancer-associated adipocytes (CAAs) or CAFs to ovarian cancer (OV) cells, where it suppresses apoptosis and confers paclitaxel resistance by downregulating its direct target, apoptotic peptidase activating factor 1 (APAF1) [67]. The impediment of APAF1 might impair caspases-initiated apoptosis, which is possibly the underlying mechanism for EV miR-21-induced chemoresistance [67–69]. All in all, EVs play a role in promoting chemoresistance by orchestrating an anti-apoptotic effect.

Furthermore, several other cellular signals, such as Wnt, Notch, signal transducer and activator of transcription 3 (STAT3), B-cell lymphoma-2 (Bcl-2), and p53, have been documented to undergo EV-induced disruptions, contributing to chemoresistance [70–73]. Intriguingly, EVs expel intracellular miR-7-5p from non-small cell lung cancer (NSCLC) cells under Everolimus stress, thereby resulting in poor prognosis via the miR-7-5p/mitogen-activated protein kinase-interacting kinase (MNK)/eukaryotic translation initiation factor 4E (eIF4E) axis [13]. This observation suggests that aberrant EV secretion can disrupt normal molecular levels within donor cells, further accentuating drug resistance.

4.1.2. Metabolic alteration

Mounting pieces of evidence have indicated the influence of metabolic alteration on drug resistance development. Glycolytic metabolic reprogramming (such as increased glucose uptake), lipid metabolic reprogramming (such as upregulated lipogenesis), and other metabolic alterations (such as redox disorder) contribute to chemoresistance [74]. EVs carrying metabolism-related non-coding RNA and metabolic key enzymes can reprogram the metabolism in recipient cells, thus promoting drug resistance. For instance, tumor-associated macrophage (TAM)-derived EV lncMMPA targets the miR-548s/aldehyde dehydrogenase 1A3 (ALDH1A3) axis to augment glucose metabolism and HCC cell multiplication [75], suggesting the effect of EV-induced metabolic alteration on malignancy. Hypoxia-induced EV pyruvate kinase M2 (PKM2) can transfer chemoresistance from cisplatin-resistant NSCLC cells to

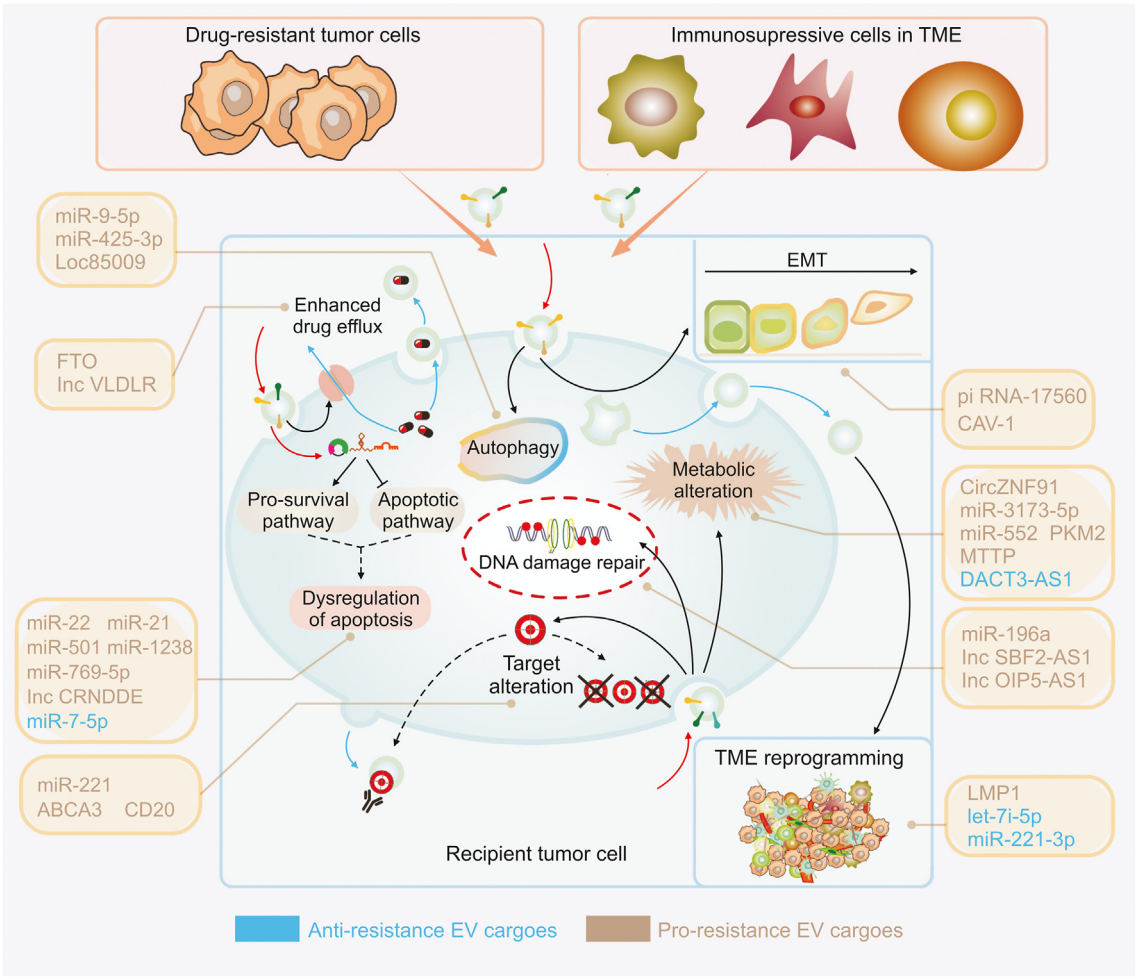

Fig. 3. The mechanisms of extracellular vesicle (EV)-mediated drug resistance in chemotherapy and targeted therapy. EVs that regulate resistance can be released by both drug-resistant tumor cells and immunosuppressive cells in tumor microenvironent (TME), thereby inducing anti-tumor drug resistance. The mechanisms include dysregulation of apoptosis, metabolic alteration, autophagy, target alteration, enhanced drug efflux, DNA damage repair, epithelial-mesenchymal transition, and TME reprogramming. The cargoes involved in EV-mediated anti-tumor drug resistance have been summarized in the sidebar, including those with promoting or inhibiting effects. EMT: epithelial-mesenchymal transition; ABCA3: ATP-binding cassette A3; PKM2: pyruvate kinase M2; MTTP: microsomal triglyceride transporter protein; LMP1: latent membrane protein 1; FTO: fat mass and obesity-associated protein; CAV-1: caveolin-1.

sensitive cells. Mechanistically, EV PKM2 augments glycolysis in recipient cells to accumulate reductive metabolites, thus neutralizing cisplatin-triggered reactive oxygen species (ROS) [72]. Again, in hypoxic conditions, circZNF91 was enriched in pancreatic cancer (PC) cell-derived EVs. EV circZNF91 transferred to PC cells promotes glycolysis and gemcitabine chemoresistance in recipient PC cells via circZNF91/miR-23b-3p/sirtuin1 (SIRT1)/HIF-1α axis [76]. Therefore, there exists an intrinsic connection among EV, hypoxia, and metabolism-associated anti-tumor drug resistance, which worth further investigation.

Ferroptosis is an iron-dependent type of cell death distinct from apoptosis, necrosis, and autophagy. Existing theories for ferroptosis initiation can be divided into the canonical glutathione peroxidase 4 (GPX4)-regulated pathway, iron metabolism pathway, and lipid metabolism pathway. The features of ferroptosis includes enhanced lipid peroxidation, increased intracellular Fe^{2+}, glutathione (GSH) depletion, or GPX4 inhibition [77]. Induction of ferroptosis combats chemoresistance while inhibition of ferroptosis correlates with chemoresistance acquisition [78]. CAF-derived EV DACT3-AS1 could restore the sensitivity of GC to oxaliplatin by enhancing oxaliplatin-mediated ferroptosis via miR-181a-5p/SIRT1 axis [77]. Inversely, CAF-secreted EV miR-522 downregulates arachidonate 15-lipoxygenase (ALOX15) expression that essentially mediates ROS production, thus enhancing chemoresistance by impeding ferroptosis in GC [79]. The dual role of CAF-derived EVs in ferroptosis and chemoresistance are shown. In pancreatic ductal adenocarcinoma (PDAC), gemcitabine co-induced CAF-secreted EVs containing miR-3173-5p but not native CAF-secreted EVs enhance chemoresistance. Mechanistically, miR-3173-5p from the CAF-secreted EVs inhibits ferroptosis by sponging acyl-CoA synthetase long chain family member 4 (ACSL4) [80]. Apart from CAF-derived EVs, Zhang et al. [81] reported that adipose-derived EV microsomal triglyceride transporter protein (MTTP) decreased polyunsaturated fatty acids ratio and lipid ROS levels and impeded ferroptosis, thus promoting oxaliplatin resistance in colorectal cancer (CRC). In summary, EVs can influence drug resistance through ferroptosis modulation.

4.1.3. Autophagy

Autophagy, a cellular process entailing sequestration, degradation, and recycling of intracellular components in a lysosome-dependent manner, is primarily triggered by nutrient deprivation and stress. The intricately regulated autophagy plays a pivotal role in upholding cellular homeostasis and bolstering cell survival.

Notably, cancer cells exhibit chronically heightened autophagy levels relative to normal cells. Therapeutic stress can further amplify this heightened autophagy, leading to the inhibition of apoptosis and the emergence of drug resistance [82–84]. Recent investigations have unveiled an association between EV release and autophagy in pharmacologically stressed tumor cells [85]. EVs have been shown to modulate autophagy, thus exerting influence over tumor progression and anti-tumor drug resistance [86].

The induction of autophagy in tumor cells can serve as a protective mechanism against the cytotoxic impacts of diverse agents. This process can be facilitated by EVs originating from drug-resistant tumor cells. To illustrate, EV miR-9-5p from tamoxifen-resistant MCF-7 cells fosters tamoxifen resistance through negative regulation of adiponectin that triggers autophagic cell death in BC [87,88]. Similarly, EV miR-425-3p obtained from NSCLC cells treated with cisplatin or cisplatin-resistant cells can transmit chemoresistance to sensitive A549 cells. This transfer occurs through the targeting of AKT1 by EV miR-425-3p, which subsequently activates autophagy by inhibiting the AKT/mTOR signaling pathway [89]. Therefore, targeting EV-mediated autophagy may be an alternative avenue in anti-tumor therapy. It's important to note that EVs don't consistently exert an unfavorable influence on autophagy, while they can also hinder autophagy to enhance drug sensitivity. For instance, Yu et al. [90] demonstrated that EV LOC85009 from lung adenocarcinoma (LUAD) cells resensitized docetaxel-resistant LUAD cells to docetaxel by hampering autophagy related 5 (ATG-5)-mediated autophagy through the ubiquitin specific peptidase 5 (USP5)/upstream stimulatory factor 1 (USF1)/ATG5 axis. All in all, both inhibiting EV-induced autophagy activation and augmenting EV-mediated autophagy inhibition are significant as potential strategies to surmount chemoresistance.

4.1.4. Enhanced drug efflux

EVs play a crucial role in drug resistance, facilitating the efflux of drugs from cells through two primary mechanisms. Firstly, they transport small regulatory molecules like miRNAs into tumor cells, influencing the expression of drug efflux transporters and amplifying drug efflux. For instance, fat mass and obesity-associated protein (FTO), an N6-methyladenosine (m6A) RNA demethylase found in EVs of resistant patients, elevates ATP-binding cassette (ABC) C member 10 (ABCC10) expression, thereby diminishing gefitinib sensitivity [91,92]. Similarly, lncRNA-VLDLR within EVs induces chemoresistance by upregulating ABC transporters associated with drug export [12]. EVs can also impact P-glycoprotein (P-gp), a membrane transporter protein capable of expelling drugs from cells, thereby undermining the efficacy of cancer treatment drugs [93]. Secondly, drugs already present within cells can be encapsulated within intracellular vesicles and subsequently expelled from the cell in an EV-dependent manner. As an illustration, cisplatin can be enclosed in secretory vesicles within melanoma cells and later secreted out via EVs [94]. Yang et al. [95] have demonstrated that CAV-1 participated in EV-mediated enhancement of TMZ efflux, thereby fostering drug resistance. Proton pump inhibitors can aid in combating cisplatin resistance by enhancing drug uptake and inhibiting EV secretion [96].

4.1.5. Target alteration

The alteration of pharmacological targets is a significant factor contributing to limited clinical outcomes in anti-tumor pharmacological therapy. Secreted EVs carrying targeted molecules can effectively sequester the therapeutic agents by acting as decoy targets, particularly in the case of monoclonal antibodies. This phenomenon has been observed in lymphoma $CD20^{+}$ EVs, which provide a protective shield against rituximab attacks. The process is regulated by the lysosome-related organelle-associated ABC transporter A3 (ABCA3), and inhibition of ABCA3 diminishes the protective effect [97]. Furthermore, changes in the number of drug targets can also lead to drug resistance, as exemplified by tamoxifen resistance. Tamoxifen, an anti-estrogen drug, competes with estradiol for ER in target organs. The interaction between tamoxifen and the ER complex modulates gene transcription and inhibits tumor cell growth. Downregulation of ER has been identified as a crucial factor in tamoxifen resistance in BC [98]. $CD63^{+}$ CAF-secreted miR-22-rich EVs have been proven to induce tamoxifen resistance in BC by impeding ER levels [59]. Additionally, the transport of miR-221/222 through EVs from tamoxifen-resistant MCF-7 cells to MCF-7 wild-type cells also contributes to resistance through the downregulation of ERα [99]. The impact of EV-mediated target alteration on anti-tumor drug resistance is supported by the aforementioned findings.

4.1.6. TME reprogramming

TME is a complex ecosystem surrounding a tumor, exerting a pivotal role in both the development and progression of tumors. EVs have the potential to elicit TME reprogramming. At the same time, TME is also constantly affecting tumor cells through EVs, which can result in either tumor promotion or inhibition. Fibroblast growth factor 2 (FGF2) is overexpressed in bone marrow stromal cells (BMSCs) of the leukemia microenvironment and secreted through EVs. This activates stromal cell-derived EV secretion via FGF2/fibroblast growth factor receptor 1 (FGFR1) signaling. Leukemia cells internalize these EVs, gaining protection against tyrosine kinase inhibitors (TKIs) like quizartinib [100]. Multiple myeloma (MM) cells and BMSCs exchange cytokines through EVs. Bortezomib treatment boosts cystine/glutamate transporter (xCT) and glutamate metabotropic receptor (GRM) expression, thereby increasing EV and glutamine secretion in both MM cells and BMSCs. By promoting MM cell migration, proliferation, and survival of MM cells via multiple signaling pathways, BMSC-derived EVs play a crucial role in bortezomib resistance [101,102]. Additionally, mounting studies have provided evidence regarding the role of tumor-derived EVs in the process of angiogenesis and EVs are involved in the failure of anti-angiogenesis therapy [23].

CAFs stand as indispensable entities within TME, exerting a profound impact on tumor growth by orchestrating processes such as proliferation, metastasis, and invasion of tumor cells [103]. CAFs influence tumor cell growth through the secretion of EVs, which are mentioned above [59,77,79]. Additionally, CAFs themselves can be modulated by EVs. Latent membrane protein 1 (LMP1), encoded by the Epstein-Barr virus (EBV), can transform normal fibroblasts (NFs) into CAFs through EV-packaged LMP1 and the NF-κB p65 pathway, promoting tumor growth [86].

M2 macrophages in TME secrete immunosuppressive factors like interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), consequently promoting both immune evasion and drug resistance in tumor cells [104]. Increasing evidence indicates that tumor-derived EVs play a role in modulating the M1/M2 polarization of macrophages [105], which transforms the effect of macrophages in inflammation and potentially contributes to anti-tumor drug resistance. Zhu et al. [106] discovered a novel pathway promoting tumor drug resistance by modulating M2 macrophages. Sonic hedgehog medulloblastoma (SHH-MB)-derived EVs with lower levels of let-7i-5p and miR-221-3p induce M2 polarization in TAMs, associated with Sonidegib resistance. Interestingly, caspase-1, a pro-inflammatory mediator at least partially transferred by EVs [107], is involved in tumor regeneration by modulating TAMs according to the work presented by Niu et al. [108]. Mechanistically,

caspase-1 cleaves peroxisome proliferator-activated receptor gamma (PPARγ), thereby augmenting the pro-tumor function of TAMs. It can be a testimony that not only apoptotic caspases influence EV-mediated drug resistance but pro-inflammatory caspase-1 may also play a role.

4.1.7. DNA damage repair (DDR)

DNA damage can disrupt the balance within cells, leading to the activation of specific biochemical pathways. These pathways are responsible for regulating cell growth, division, DNA replication, and repair processes, which maintain tumor cell survival and pose a significant threat to anti-tumor drug resistance [109]. EVs can induce DDR processes in tumor cells via cargo transfer. Recent evidence has indicated the relevance between EV-mediated DDR and anti-tumor drug resistance. In the case of GBM cells resistant to TMZ, the transfer of drug resistance to sensitive cells is facilitated through EVs enriched with lncSBF2-AS1. lncSBF2-AS1 functions as a competing endogenous RNA (ceRNA) for miR-151a-3p, leading to an enhancement in double-strand break (DSB) repair and the promotion of chemoresistance [110]. Additionally, trastuzumab-resistant cells exhibit elevated levels of lncRNA OIP5-AS1. The transfer of OIP5-AS1 via EVs induces an increase in high mobility group box 3 (HMGB3) expression by acting as a sponge for miR-381-3p in the recipient cells [111]. HMGB3, a DNA-binding protein, manifests overexpression across various cancers, playing a significant role in the regulation of DDR [112]. The increased level of HMGB3 mediated by EVs potentially contributed to the development of drug resistance. Moreover, in mixed-lineage leukemia, resistance to proteasome inhibitors (PIs) can be transferred to sensitive cells from tumor cells under therapy stress, by inducing cell cycle arrest and enhancing stemness in an EV-dependent manner [113]. Besides EVs with tumor origins, CAF-derived EV miR-196a was also reported to cause the downregulation of cyclin-dependent kinase inhibitor 1B (CDKN1B) and inhibitor of growth family member 5 (ING5) genes in head and neck tumor cells, leading to DDR and ultimately fostering cisplatin resistance [114]. In summary, EVs have been found to play a crucial regulatory role in DDR mechanisms within tumor cells, associated with the development of drug resistance.

4.1.8. Epithelial-mesenchymal transition (EMT)

Traditional therapies typically target the majority of the non-cancer stem cell (nCSC) population while sparing the smaller subsets of cancer-stem cells (CSCs), creating a potential scenario for future local disease recurrence and/or the emergence of metastases [115]. The process of EMT appears to be a significant strategy employed by carcinoma cells to adopt a CSC phenotype and realize metastasis [116]. Additionally, the EMT program plays a crucial role in conferring resistance to various therapeutic agents across multiple cancer types [117]. In parallel, an increasing number of researches have reported that EVs promote cancer EMT and metastasis, thereby contributing to drug resistance [118,119]. Lin et al. [118] have demonstrated that CAV-1 in tumor-derived EVs acted as a potent driver to induce CSC phenotypes and EMT in prostate cancer (PCa) undergoing neuroendocrine differentiation through the NF-κB signaling pathway. Moreover, Ou et al. [119] have reported that senescent neutrophils produce an increased number of EVs, which confer drug resistance to tumor cells *in vitro* and *in vivo*. Mechanistically, senescent neutrophils-derived EV piRNA-17560 enhances the expression of FTO in BC cells. The upregulation of FTO further strengthens ZEB1 transcript stability and expression by decreasing m6A RNA methylation, leading to EMT and chemoresistance of tumor cells [119]. Notably, the increased expression of lysophosphatidic acid receptor 4 (LPAR4) in tumor cells under stress such as chemotherapy, has been proven to promote tumor initiation, stemness, metastasis, and drug resistance. Mechanistically, the induction of the LPAR4/AKT/cyclic adenosine monophosphate response element binding protein (CREB) axis enables the formation of a fibronectin-rich extracellular matrix, thus creating a new tumor-initiating niche [120,121]. Meanwhile, lysophosphatidic acid (LPA), the ligand of LPAR4, can partition into EV membrane [122], potentially stimulating LPAR4-induced drug resistance, which is noteworthy.

4.2. Resistance to immunotherapy

Immunotherapy, which sparks great optimism among cancer patients, acts by restoring the immunosuppressive TME shaped by tumors and reactivating anti-tumor immunity. Represented by immune checkpoint blockade (ICB) and adoptive cell transfer, this rising therapy exhibits the potential to induce enduring regression in refractory tumors, even those resistant to other treatments [123,124]. Immune checkpoint inhibitors (ICIs), targeting checkpoints like programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on T cells, have demonstrated clinical efficacy across diverse cancers [125]. Nevertheless, despite the advancements of immunotherapy, favorable outcomes from immunotherapy remain elusive for many patients due to various factors [126]. Recently, rapidly increasing publications based on EVs in immunotherapy provide new perspectives to comprehend the mechanisms underlying immunotherapy resistance (Fig. 4).

4.2.1. EV-mediated T-cell dysfunction

Immunosuppression is a key contributor to ICB failure, and emerging evidence highlights the immunosuppressive role of EVs within the TME [127]. Circulating EVs in metastatic melanoma patients have been shown to dampen nivolumab-induced activation of peripheral blood mononuclear cells (PBMCs). Notably, EVs derived from non-responders to anti-PD-1 therapy exhibit greater suppression of PBMCs than those from responders [128].

Our pioneering study suggests that elevated levels of EV-bound programmed death-ligand 1 (PD-L1) correlate with T cell exhaustion, undermining T cell re-invigoration in response to anti-PD-1 therapy [129]. Furthermore, tumor-derived EV PD-L1 can impede T cell activation in draining lymph nodes, impairing systemic anti-tumor immunity. Interestingly, EV PD-L1 appears resistant to anti-PD-1 antibodies [130]. Mechanistically, by binding to PD-1 on T cells, EV PD-L1 inhibits their activation and hampers their cytotoxic function via the PD-L1/PD-1 signaling pathway [131]. The interactions between EV PD-L1 and plasma membrane PD-1 have been observed in various cancers, including melanoma [129,132], lymphoma [133], and BC [91]. The mentioned findings underscore the crucial role of PD-L1$^+$ EVs in anti-PD-1 resistance by inducing T-cell dysfunction. Additionally, ERK-induced phosphorylation of hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) selectively enriches PD-L1 in melanoma cell-derived EVs. EVs with heightened phosphorylated HRS (p-HRS)-bound PD-L1 migrate to the local TME, obstructing CD8$^+$ T cell infiltration and promoting resistance to anti-PD-1 antibodies [134].

Beyond PD-L1, various RNAs and proteins carried by EVs also contribute to anti-PD-1 resistance by inducing T-cell exhaustion. For instance, EV-mediated delivery of circular RNA ubiquitin-specific peptidase 7 (circUSP7) disrupts CD8$^+$ T lymphocyte function through circUSP7/miR934/src homology 2 domain containing protein tyrosine phosphatase 2 (SHP2) signaling, ultimately conferring resistance to anti-PD-1 treatment in NSCLC [135]. Furthermore, when internalized by CD8$^+$ T cells, EV circCCAR1

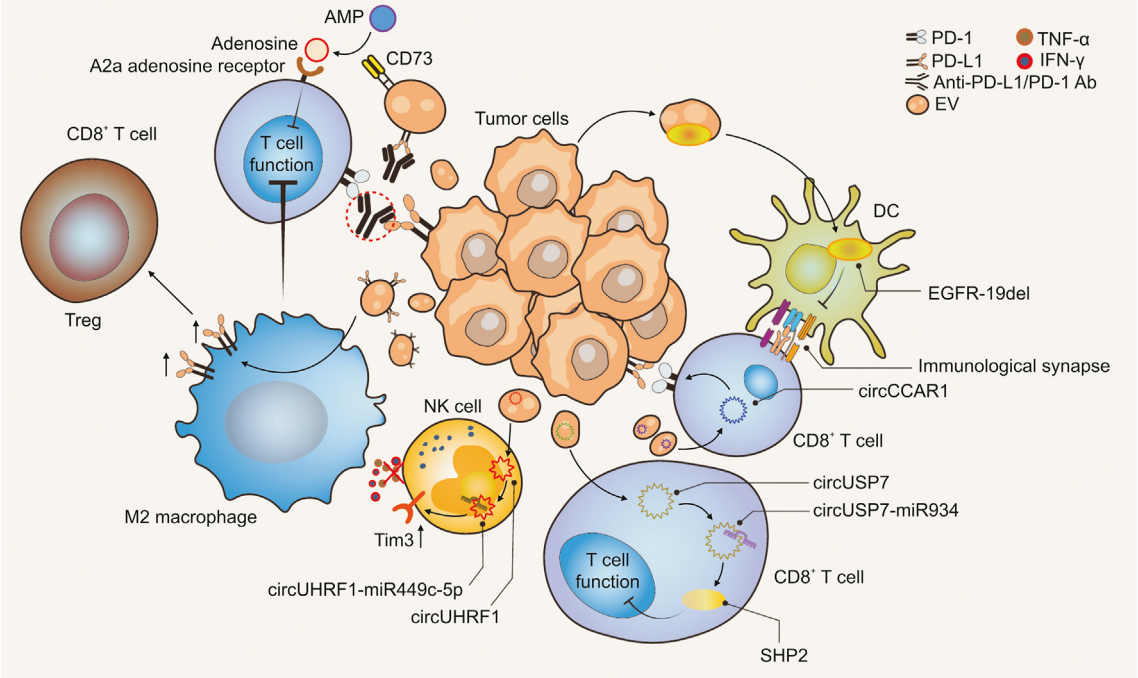

Fig. 4. The mechanisms of extracellular vesicle (EV)-mediated drug resistance in immunotherapy. EVs originating from tumor cells can cause dysfunction of $CD8^+$ T cells, reprogram stromal cells and other immunocytes in tumor microenvironment, and act as decoys for antibodies, thus forming resistance to immunotherapy. Tim3: T cell immunoglobulin and mucin domain-3; Treg: regulatory T cell; NK: natural killer; AMP: adenosine 5′-monophosphate; DC: dendritic cell; EGFR: epidermal growth factor receptor; circUSP7: circular RNA ubiquitin specific protease 7; PD-L1: programmed death-ligand 1; PD-1: programmed cell death protein 1; TNF-α: tumor necrosis factor-alpha; IFN-γ: interferon-gamma; Ab: antibody; EV: extracellular vesicle; SHP2: src homology 2 domain containing protein tyrosine phosphatase 2.

curtails proteasomal degradation of PD-1 on T cells, thus hindering $CD8^+$ T cell function and promoting immunotherapy resistance [136]. Additionally, EV CD73 functions as an AMPase that converts adenosine monophosphate (AMP) into adenosine. Then adenosine binds to A2a adenosine receptors on T cells, suppressing effector functions and conferring resistance to anti-PD-1 therapy [137].

4.2.2. Reprogramming stromal cells and other immunocytes

The role of EVs in immunotherapy resistance extends beyond T-cell dysfunction. EV-mediated cell-to-cell communication can modify the phenotypes of stromal cells and other immunocytes besides T cells, thereby contributing to immunotherapy resistance. For example, BC cells transmit EV PD-L1 to other tumor cells, macrophages, and dendritic cells, influencing immunosurveillance within the TME [131]. Moreover, $PD\text{-}L1^+$ EVs induce a tolerogenic-like phenotype in antigen-presenting cells (APCs) by upregulating PD-L1, intercellular adhesion molecule-1 (ICAM-1), and major histocompatibility complex class I (MHC-I) expression [138]. Treatment of melanoma with an xCT inhibitor leads to heightened PD-L1 levels in secreted EVs, enhancing PD-L1 expression in macrophages, inducing M2 polarization and contributing to the failure of anti-PD-1/PD-L1 treatment [139]. In HCC, elevated levels of plasma EV circUHRF1 drive anti-PD-1 therapy resistance by reducing NK cell proportions and hindering tumor infiltration. Mechanistically, EV circUHRF1 suppresses NK cell interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) production by upregulating T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) expression via miR-449c-5p degradation [140]. Additionally, tumor cells carrying EGFR-19del mutation transfer EGFR-19del protein to dendritic cells (DCs) through EVs, downregulating costimulatory molecule expression and impairing DC priming of $CD8^+$ T cells in lymph nodes. This results in reduced T-cell infiltration at the tumor site and promotes anti-PD-1 resistance [141].

4.2.3. Antibody decoys

Furthermore, EVs can act as decoys, competitively binding to antibodies and neutralizing their effects. Circulating EVs in metastatic melanoma patients have been found to bind and neutralize nivolumab, contributing in part to anti-PD-1 therapy resistance [128]. Chen et al. [142] discovered that tumor-derived EVs could decoy anti-PD-L1 antibodies through PD-L1 on the EV membrane. EV-bound anti-PD-L1 antibodies (αPD-L1) are more rapidly phagocytosed by macrophages than free αPD-L1, offering insights into the mechanism of anti-PD-L1 resistance induced by tumor-derived EV PD-L1.

4.3. Resistance to radiotherapy

Radiotherapy is a significant conventional approach for treating tumors, which involves the use of radiation to induce DNA damage in tumor cells. Additionally, the combination of radiotherapy with anti-tumor drugs is considered a viable strategy for achieving enhanced therapeutic outcomes [143,144]. Despite its potential benefits, radiotherapy can be hampered by instances of radioresistance, which can result in cancer recurrence in certain patients [145].

Multiple studies have indicated that radiation promotes the secretion of higher levels of EVs by cells. These radiation-induced EVs exhibit differences in properties such as zeta potential, protein profile, miRNA profile, and even in their ability to be taken up by recipient cells, compared to their non-irradiated counterparts [146–151]. More importantly, EVs produced by irradiated tumor cells can induce radiotherapy resistance by delivering highly expressed malignant-associated molecules to non-irradiated tumor cells [152]. Furthermore, radiation-induced EVs may favor an immunosuppressive TME to confer radioresistance. For instance, irritated BC cells secret high level of EV TGF-β1 to promote Treg differentiation and tumor infiltration [148].

DDR is widely recognized as a primary mechanism contributing to the development of resistance in radiotherapy, and EVs also contribute to this phenomenon. Hypoxia induces the secretion of EVs with elevated expression of miR-340-5p in esophageal squamous cell carcinoma cells, which promote cell survival and accelerate DDR by targeting the KLF10/UVRAG axis in normoxic tumor cells [153]. EV miR-194-5p from dying PC cells promotes the survival of tumor repopulating cells by inducing G1/S arrest and facilitating DDR, which contributes to radioresistance [154]. Moreover, EVs mediate radioresistance through mechanisms such as promoting autophagy [155] and impairing caspase cascade in tumor cells [156].

5. EV-based strategies against drug resistance

Extensive research, including the aforementioned studies, has demonstrated that EVs serve as propagators of anti-tumor drug resistance. It is imperative to capitalize on the biological characteristics of EVs and develop relevant therapeutic strategies to effectively combat anti-tumor drug resistance.

5.1. Biomarkers for drug resistance prediction

EVs secreted by all types of living cells are detectable in body fluids, including blood, urine, saliva, and ascites. They are increasingly being recognized as non-invasive biomarkers in liquid biopsy, conveying crucial information from donor cells for assessment, and showing significant relevance to their parental cells and tissues [157,158]. Notably, analyzing tumor-derived EVs could provide deeper insights into the overall tumor mutational landscape, potentially enhancing treatment decisions and overcoming the spatial heterogeneity limitation seen in tissue biopsies [159]. Moreover, compared to other biomarkers in liquid biopsy, such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), EVs exhibit higher plasma concentration, enhanced stability, cost-effectiveness, and ease of repeatable detection [160,161]. These characteristics position EVs as promising biomarkers in liquid biopsy. Numerous studies have utilized EVs for cancer diagnostics, prognostics, therapy response prediction, and anticipating therapy resistance [161]. Predicting treatment response based on EVs can help combat drug resistance and inform pre-therapy decisions for optimal treatment selection.

Among the diverse EV-based biomarkers reported, EV PD-L1 emerges as a noteworthy marker for predicting response to ICIs. Our groundbreaking research unveils that EV PD-L1 mediates immunosuppression and correlates with anti-PD-1 response. Metastatic melanoma patients with elevated pre-treatment circulating EV PD-L1 exhibited poorer responses to pembrolizumab treatment. Intriguingly, circulating EV PD-L1 levels significantly increased during pembrolizumab therapy, particularly within the initial 6 weeks. However, patients showing a greater increase in circulating EV PD-L1 levels at 3–6 weeks demonstrated a more favorable response to anti-PD-1 therapy [129]. Another study centered on advanced NSCLC observed that higher pre-therapy levels of total small EV protein (TEP) were linked to poorer progression-free survival (PFS) and overall survival (OS) in patients undergoing ICI treatment [162]. Additionally, an increase in EV PD-L1 was evident in non-responders relative to responders, serving as an independent biomarker for worse prognosis in NSCLC patients receiving ICI [163]. In summary, both the baseline and dynamic changes in EV PD-L1 levels hold promise as potential biomarkers for predicting drug resistance. Interestingly, recent studies have revealed that only circulating EV PD-L1 shed from tumor cells functions as an independent biomarker for predicting the response to anti-PD-1 therapy [128,164], surpassing the utility of total EV PD-L1 in the bloodstream. It raises the concern of specifically detecting PD-L1 on the tumor-derived EV subpopulation to predict immunotherapy response.

Beyond EV proteins like PD-L1, EV RNA also offers potential for EV-based biomarkers. Previous studies have identified significant alterations in various miRNAs during tumor progression and prognosis [165]. For instance, in advanced EGFR/anaplastic lymphoma kinase (ALK) wild-type NSCLC patients undergoing anti-PD-1 therapy, EV hsa-miR-320d, hsa-miR-320c, and hsa-miR-320b were notably upregulated in progressive disease (PD) groups compared to the partial response (PR) group before treatment initiation [166], suggesting their potential as predictive markers for therapy response and circumventing drug resistance. Another study combined the assessment of EV Let-7b-5p, miR-184, and circulating miR-22-3p levels in NSCLC patients to prognosticate and predict oxaliplatin resistance, effectively distinguishing patients with oxaliplatin resistance who might benefit from osimertinib/AKT blockade combination treatments [159]. The EV-based biomarkers for predicting drug response are summarized in Table S2 [11,71,89,128,129,157,159,162,163,166–176].

5.2. Targeted inhibition of EVs

As mentioned earlier, the biogenesis and secretion of EVs is a finely regulated process, involving numerous regulatory factors. The levels of EVs released by cells can be modulated through targeted inhibition of these regulators. Under therapeutic stress, Drug-resistant tumor cells and tumor-associated immunosuppressive cells release EVs that contribute to drug resistance in anti-tumor therapy. Aiming at improving therapy outcomes, inhibiting EV biogenesis and secretion holds promise to reverse EV-mediated drug resistance. For instance, combination treatment with bortezomib and the nSMase2 inhibitor GW4869 demonstrated a stronger anti-tumor effect than either agent alone [113], indicating the potential of EV inhibitors in refining anti-tumor therapy.

EV PD-L1 has been identified as a negative factor in immunotherapy resistance. Inhibition of EV biogenesis and secretion during immunotherapy could diminish immunosuppression as well as mitigate the depletion of anti-PD-L1 antibodies caused by EV PD-L1. Research has demonstrated that genetic knockdown of Rab27a and treatment with the EV inhibitor GW4969 amplified the therapeutic impact of anti-PD-L1 antibodies [131]. Macitentan (MAC) downregulated tumor-derived EV PD-L1 release by targeting endothelin receptor A (ETA) on tumor cells, resulting in enhanced $CD8^+$ T cell cytotoxicity. The combination therapy of MAC and anti-PD-L1 antibodies heightened the anti-tumor response and triggered enduring memory immunity [177]. Yan et al. [178] employed engineered self-adaptive platelets to co-deliver EV-inhibiting siRNA and anti-PD-L1 antibodies. This delivery system impeded EV PD-L1 level by silencing Rab27a, thereby mitigating immunosuppression and sensitizing ICI therapy. The significance of inhibiting EVs to restore T cell function in combating immunotherapy resistance, which is attributed to EV PD-L1, has been demonstrated.

Intriguingly, a recent study revealed that IFN-γ activated $CD8^+$ T cells promote tumor cell lipid peroxidation and ferroptosis [179], which indicated an enhanced ferroptosis of tumor cells after restoration of T cell functions. Inspired by this finding, Wang et al. [180] attempted co-delivery of the ferroptosis inducer Fe^{3+} and GW4869 to the tumor. This delivery system induced systemic anti-tumor immune responses by diminishing EV PD-L1-mediated immunosuppression and helped amplify ferroptosis, thus bolstering the efficacy of anti-PD-L1 therapy. Similarly, GW4869-induced EV inhibition, when coupled with photothermal therapy and Fe^{3+}-induced ferroptosis, augmented immunotherapy outcomes by enhancing ferroptosis [181].

Beyond established regulators of EV biogenesis and secretion, such as Alix, nSMase, and Rab27a, new targets have been explored to enhance therapeutic efficacy. For instance, ubiquitin-conjugating enzyme E2O (UBE2O) decreased EV secretion by disrupting caveolae formation through the ubiquitination and degradation of CAV-1. Augmenting UBE2O may offer a strategy to hinder EV secretion [182]. Transient receptor potential mucolipin3 (TRPML3), prominently expressed in resistant NSCLC cells, promotes EV release via sustained Ca^{2+} release. Deletion of TRPML3 restored gefitinib sensitivity in resistant cells [10]. Inhibiting ABCA3 with indomethacin impeded robust EV release in aggressive B-cell lymphoma and restored lymphoma cell susceptibility to rituximab-induced lysis. This inhibition also curtailed EV-mediated anti-CD20 antibody binding and complement consumption [183,184]. Targeting the FGF2/FGFR axis to inhibit stromal EV release reduced stromal growth and alleviated EV-mediated protective effects on leukemia cells during TKI treatment [100]. All in all, the identification of potent targets will shed light on EV inhibition to surmount anti-tumor drug resistance.

In summary, inhibiting EV biogenesis and secretion presents a promising strategy to overcome resistance in chemotherapy, targeted therapy, immunotherapy and even radiotherapy.

6. Challenges and future perspectives

6.1. Isolation of EV subpopulations for accurate biomarker detection

Given the pivotal role of EVs in resistance to anti-tumor drugs, the pre-detection of specific drug-resistant molecules in EVs to predict drug resistance would greatly improve clinical decision-making. However, the clinical application of EV-based biomarkers faces the challenges of EV heterogeneity. EVs are heterogeneous groups secreted by a diverse range of cells. Research on mechanisms of EV-mediated anti-tumor drug resistance has identified that some oncogenic molecules in EVs from certain cell sources induced resistance. However, it should be noted that these oncogenic molecules might also be present in EVs secreted by other cell types, possibly without the capability to develop resistance. Therefore, accurate prediction of drug resistance requires targeted detection of molecules within specific EV subpopulations. Unfortunately, current techniques, such as reverse transcription quantitative polymerase chain reaction (RT-qPCR) for EV RNA detection and western blot (WB) for EV protein detection, only allow for non-specific detection of certain drug-resistant molecules in total EVs without discriminating their cellular origins, which may adversely affect the accurate prediction of treatment efficacy.

Consequently, we propose the separation of EV subpopulations derived from specific cell sources before the detection of EV biomarkers to enhance predictive accuracy. To address this issue, our group has developed a non-contact method to isolate tumor-derived EV subgroups by eliminating those originating from non-tumor cells [185]. This method holds promise in providing a naturally occurring tumor-derived EVs for subsequent detection of tumor-source-specific drug-resistant molecules (Fig. 5A).

6.2. Targeting EVs as therapeutic strategies

6.2.1. Specifically inhibiting drug resistance-promoting EV (DR-EV) biogenesis and secretion

Inhibition of EV biogenesis and secretion, employing both genetic editing and pharmacological interventions, holds great promise as a prospective therapeutic approach. However, several challenges persist in the clinical translation of this strategy [8,186].

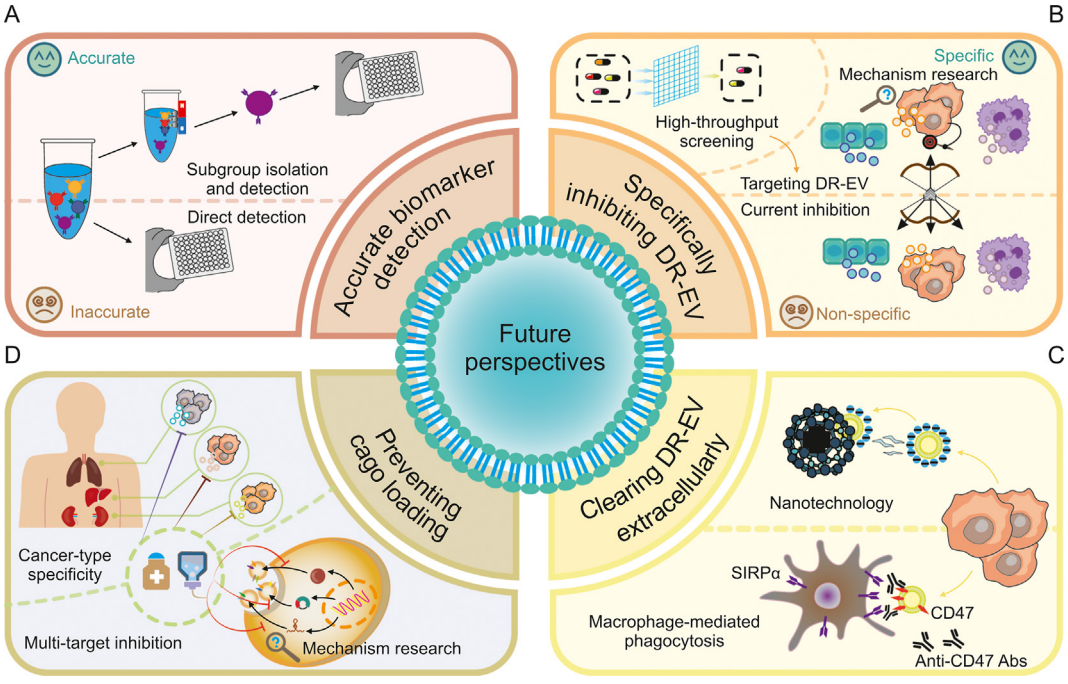

Fig. 5. Future perspectives in overcoming extracellular vesicle (EV)-mediated drug resistance to anti-tumor therapy. (A) Increasing the accuracy of drug resistance prediction can be achieved through the detection of biomarkers after separating EV subpopulations. (B) Specifically inhibiting the biogenesis and secretion of drug resistance-promoting extracellular vesicles (DR-EVs) can safely and effectively overcome EV-mediated drug resistance. High-throughput drug screening is an effective approach for discovering inhibitors targeting EV subpopulations. (C) Another approach to overcome EV-mediated drug resistance is the clearance of DR-EVs through nanotechnology or macrophage-mediated phagocytosis in the extracellular environment. (D) Inhibiting oncogenic EV cargo loading through the development of inhibitors with cancer-specific and multitarget inhibitory capabilities is a promising therapeutic approach. This strategy requires a mechanistic understanding of drug-resistant cargo loading as a foundation for research. SIRPα: signal regulatory protein alpha; Ab: antibody.

EVs consist of heterogeneous populations, while only a specific subset of EV subgroups, mostly originating from drug-resistant tumor cells and immunosuppressive tumor-associated cells, contribute to drug resistance. Inhibition of EVs involved in maintaining homeostasis may have unintended consequences on the human body. However, when it comes to common pharmacological EV inhibitors, they target universal regulators that govern EV biogenesis and secretion in all cell types. Existing EV inhibitors like GW4869, act by non-specifically inhibiting the basal level of EV release, ignoring distinct EV subpopulations. Gene editing also poses similar concerns, as it often targets universal regulators of EV biogenesis and secretion, such as Rab27a, which non-specifically depletes EVs secreted by all cells. In addition, gene editing technologies themselves raise safety concerns, including off-target effects resulting in deletion or mutation of non-targeted genes, immune response and the insertion of viral genomes into the host genome caused by using viral vectors, and more [187,188].

Nonspecific inhibition of EVs may pose unnecessary adverse effects on the body, serving as a significant obstacle to the clinical translation of this therapy. Hence, the future focus is on specifically inhibiting the biogenesis and secretion of DR-EVs, as a promising approach to effectively and safely overcome anti-tumor drug resistance. More concerted efforts should be directed toward exploring the distinctive mechanisms and regulatory factors that govern the biogenesis and secretion of the DR-EV subpopulation. Mechanism findings will provide potential targets for achieving precise inhibition of the DR-EV subpopulation while sparing other EVs. Notably, researchers are exploring the possibility of conducting high-throughput screening among clinically approved drugs to identify EV subpopulation-specific inhibitors [189], based on the identified regulators governing the biogenesis and secretion of EV subpopulations such as tumor-derived EVs. This strategy holds great promise as it bypasses laborious exploration and ensures safety, harboring potent practical value for inhibiting EV biogenesis and secretion (Fig. 5B).

6.2.2. Clearing DR-EVs in extracellular space

Investigating the intricate mechanisms underlying the biogenesis and secretion of distinct EV subpopulations is time-consuming and labor-intensive. An alternative approach to mitigating the detrimental effects of DR-EVs is to clear them in the extracellular space, which circumvents the arduous process of exploring the mechanisms involved. Macrophage-mediated phagocytosis has been recognized as a crucial mechanism for the clearance of EVs and plays a role in determining EV concentration in the bloodstream [190,191]. “Don't eat me” signal proteins (such as CD47/signal regulatory protein alpha (SIRPα)) and “Eat me” signal (such as phosphatidylserine (PS)/phosphatidylserine receptor (PSR)) act as regulatory roles in macrophage-mediated phagocytosis [192]. Harnessing macrophage-mediated phagocytosis for EV clearance, such as the blockade of CD47 on EVs, holds promise to boost the elimination of unwanted EVs. Despite the potential use of macrophage-based EV clearance, the clearing specificity for the DR-EV subpopulation remains a crucial aspect in the advancement of this therapeutic approach. Avoiding non-specific clearance of all EVs is desirable and futuristic effort is needed to realize specific phagocytosis of DR-EV subpopulations.

On the other hand, targeted clearance of DR-EVs using nanotechnology holds promise as another prospective approach. Xie et al. [193] designed a positively charged mesoporous silica nanoparticles (MSNs) functionalized with EGFR-targeting aptamers (MSN-AP), which could specifically recognize and bind negatively charged circulating oncogenic EVs. The conjugates of MSN-APs and oncogenic EVs were efficiently eliminated from the bloodstream and transported to the intestine, resulting in successful clearance of the oncogenic EVs. This study provides a paradigm for future research on the specific clearance of DR-EV subpopulations (Fig. 5C).

6.3. Preventing oncogenic cargo loading in EVs

Oncogenic cargoes play a pivotal role as a mediator in EV-mediated drug resistance. Suppressing the selective sorting and loading of oncogenic cargo into EVs represents a highly promising yet under-researched strategy, in addition to inhibition of EV biogenesis and secretion. For instance, inhibition of enhancer of zeste homolog 2 (EZH2)/STAT3 signaling strongly depletes the loading of oncogenic cargoes into EVs, thereby overcoming chemotherapy-elicited EV-induced drug resistance [70]. By blocking TGF-β, the PD-L1 enrichment in tumor-derived EVs is diminished, which subsequently reverses T cell dysfunction [194]. We have identified the critical regulatory role of HRS in EV PD-L1 secretion. By knocking out HRS, we can reduce the circulating levels of sEV PD-L1, thereby increasing the tumor infiltration of $CD8^+$ tumor-infiltrating lymphocytes and the efficacy of anti-PD-1 therapy in head and neck squamous cell carcinoma [195].

However, current understanding of the intricate mechanisms governing cargo sorting and loading remains limited, which poses a significant obstacle to the advancement of relevant drug development efforts. To overcome this challenge, further elucidation of these mechanisms in future research endeavors is crucial to identify specific targets for effectively inhibiting oncogenic cargoes in EVs. Furthermore, it is important to note that the composition of drug-resistant EV cargo varies across different types of cancer. Even within the same cancer type, multiple EV cargoes contribute to resistance against anti-tumor drugs. This inherent complexity adds an additional difficulty to the development of effective therapeutics. Therefore, exploring cancer-type-specific cargo inhibition therapies that target multiple specific cargoes represents a promising avenue to overcome anti-tumor drug resistance (Fig. 5D).

7. Conclusion

In this review, we provide a comprehensive overview of the mechanisms responsible for anti-tumor drug resistance in chemotherapy, targeted therapy, immunotherapy and even radiotherapy. Specifically, intrinsic characteristics of EVs make them excellent biomarkers for predicting drug resistance. Additionally, we focus on the potential of targeted inhibition of EVs as a promising therapeutic approach to counteract EV-induced drug resistance. Furthermore, we discuss the key challenges associated with anti-tumor drug resistance, particularly in the context of EVs, and propose potential avenues for future research.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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