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Review

Enigmatic exosomal connection in lung cancer drug resistance

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Lung cancer remains a significant global health concern with limited treatment options and poor prognosis, particularly in advanced stages. Small extracellular vesicles such as exosomes, secreted by cancer cells, play a pivotal role in mediating drug resistance in lung cancer. Exosomes have been found to facilitate intercellular communication by transferring various biomolecules between cancer cells and their microenvironment. Additionally, exosomes can transport signaling molecules promoting cancer cell survival and proliferation conferring resistance to chemotherapy. Moreover, exosomes can modulate the tumor microenvironment by inducing phenotypic changes hindering drug response. Understanding the role of exosomes in mediating drug resistance in lung cancer is crucial for developing novel therapeutic strategies and biomarkers to overcome treatment limitations. In this review, we summarize the current knowledge on conventional and emerging drug resistance mechanisms and the involvement of exosomes as well as exosome-mediated factors mediating drug resistance in lung cancer.

INTRODUCTION

Lung cancer remains a significant health concern accounting for a substantial number of cancer-related deaths despite advancement in treatment modalities. Therapy resistance is considered as a major concern contributing to the poor survival rates of lung cancer patients. Several mechanisms like phenotypic heterogeneity, apoptotic bypass, metabolic reprogramming, epithelial-mesenchymal transition, enhanced angiogenesis, increased drug efflux, and decreased drug intake, are responsible determinants and major modulators of drug resistance in lung cancer.[1] From the past decade, new investigations on exosomes have found them to be transporter vehicles in cellular communication and major modulators of drug resistance.[2,3]

Exosomes are types of small extracellular vesicles of size ranging from 30 to 200 nm, secreted by almost all cells including cancer cells. These nanovesicles once thought to be the "cellular waste," are now realized to be acting as molecular players in regulating multiple biological functions and assisting as a cargo in cellular communication and transport by delivering lipids, proteins, and nucleic acids to neighboring as well as distant cells.[4] Recent investigations propose that cancer stem cells could be a responsible mediator, intervening in drug resistance, influencing neighboring cells via exosomes. Also some evidence suggests that cancer-derived exosomes act as a promoter in different cancers such as breast cancer, oral cancer, cervical cancer, and colorectal cancer.[5–7] Nevertheless, there has been limited exploration into the potential influences of exosomes in the microenvironment of lung cancer and their contribution to drug resistance. This review summarizes emerging drug resistance mechanisms along with the cross-signaling between exosomes secreted by heterogeneous populations of cancer cells and how they modulate drug resistance in bystander and distant cells by transporting various factors in the lung tumor microenvironment (TME). Also these exosomes may be assisting via autocrine or paracrine signaling to the cancer cell and regulate the tumor microenvironment. This will provide new therapeutic strategies and targeted therapy options focusing on exosomes that have the potential to overcome drug resistance in lung cancer.

DRUG RESISTANCE MECHANISMS IN LUNG CANCER

Drug resistance is a common and formidable obstacle in the treatment of lung cancer. Despite significant advances in therapy, cancer cells can develop different mechanisms to evade the effects of chemotherapy drugs and targeted therapies. In the context of drug resistance, exosomes have been implicated in several mechanisms and transfer of drug resistance proteins, nucleic acids, survival signal molecules, and genetic materials and lipids to bystander cells. Additionally, cancer cells can develop efflux pumps that may be transferred via exosomes, reducing their concentration within the cells. Altered drug metabolism and the presence of heterogeneous cancer cell populations within tumors further contribute to drug resistance.[8] There are several different mechanisms involved in drug resistance mechanisms in lung cancer, such as TME remodeling, tumor heterogeneity, drug inactivation, reduced drug uptake, and increased drug efflux.[9,10] But the role of exosome involvement in resistance mechanisms is a little obscured, so this review will solely focus on the implications of exosomes in drug resistance mechanisms in lung cancer. Following are some of the traditional and emerging mechanisms such as phenotypic heterogeneity, metabolic reprogramming, TME remodeling, apoptotic evasion, and epithelial-to-mesenchymal transition (EMT) associated with exosomes that may uncover several pathways for the targeted therapies and therapy resistance in lung cancer.

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PHENOTYPIC HETEROGENEITY AS A PERVASIVE FEATURE: CAN EXOSOMES MODULATE THE PHENOTYPIC CHARACTERS?

Cancer cells often exhibit plasticity, allowing them to switch between different phenotypic states according to their influential environment. This phenotypic plasticity can lead to the emergence of drug-resistant subpopulations. However, cancer cells may undergo an EMT, transforming to a more invasive and drug-resistant phenotype. Conversely, cells can also undergo a mesenchymal-to-epithelial transition (MET), leading to increased sensitivity to certain therapies. This phenotypic switching contributes to the dynamic nature of drug resistance in cancer.[11]

Recent investigations suggest that phenotypic heterogeneity may play a role in drug resistance in cancer that explains the occurrence of "contrasting" cells within an isogenic population. Those cells show a different expression profile of phenotypic changes from the remainder of the population.[12] It depends upon cell intrinsic and extrinsic factors that play a significant role in drug resistance. Dynamic phenotypic switching may occur when the drug-tolerant cells act like "persister cells" to affect neighboring cells and instruct via exosomes, to become resistant against chemotherapy. Resistant cells can become sensitive after the lower dose of chemotherapeutic treatment showing the intercellular signaling to change in phenotypes that may transform sensitive cells to resistant cells via exosomes.[13] Experimental findings indicate that transforming growth factor (TGF)-β induced cytoskeletal remodeling and phenotypic heterogeneity in non-small cell lung cancer (NSCLC) cells, which leads to increased cellular stiffness and migratory capabilities, that could serve as potential targets for pharmaceutical interventions of lung cancer.[14] Also some reports suggest that TGF-β can be transported via exosomes while exosomes derived from dormant cancer cells can transfer dormancy-inducing signals to other cancer cells, promoting the acquisition of a dormant phenotype.[15] Dormant cells are often less responsive to chemotherapy and targeted therapies, contributing to drug resistance. In addition, exosomes can transfer proteases, such as MMPs (matrix metalloproteinase-1) and tissue inhibitors of metalloproteinase (TIMPs), which regulate the balance of ECM degradation and synthesis changing the phenotypes. Increased MMP activity promotes ECM remodeling, facilitating tumor invasion and metastasis and phenotypic remodeling possibly via exosomes.[16] This evidence suggests that exosomes might have a role in promoting phenotypic switching, which has a role in therapeutic resistance in lung cancer.

Studies have revealed that phenotypic transformation of lung cancer subtypes into small cell lung cancer (SCLC) occurs in approximately 3%–15% of patients who exhibit clinical indications of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) by osimertinib.[17] Earlier studies on EGFR gene sequencing have demonstrated that a potential phenotypic transformation from NSCLC to SCLC in some tumors.[18] Transportation of EGFR via exosomes might have a role in promoting the resistance mechanisms in NSCLC contributing to drug resistance. Still there is no clearer evidence of phenotypic transformation developed by chemotherapeutic treatments via exosomes that may lead to drug resistance in lung cancer. Additionally, there might be some underlying mechanisms where exosomes may play a role in transporting different factors altering phenotypes modulating TME in lung cancer. Understanding the sources and underlying regulatory mechanisms regulated by exosomes and how they are correlated with metabolic reprogramming could provide key insights to help in improving the treatment of lung cancer.

METABOLIC REPROGRAMMING AS A NEW EMERGING MECHANISM: CAN EXOSOMES RE-WRITE METABOLIC NEED OF CANCER CELLS?

Metabolic reprogramming is recognized as an emerging hallmark of cancer cells in recent years. It is an important aspect of cancer cells where they reprogram the microenvironment according to the need of nutrients, energy, redox force for rapid proliferation, and supposedly drug resistance. Metabolic reprogramming via glucose, amino acid, lipid, and cholesterol metabolism tends to be involved in rewiring the cancer cells into resistant cells by diverse mechanisms. Various glycolytic enzymes like PFK1, PKM2, and LDH are shown to be involved in glycolytic reprogramming of cancer cells that leads to drug-resistant cells via exosomes.[19,20] In a recent discovery, it was revealed that Nrf2 is involved in metabolic reprogramming in NSCLC and was found to be transported via exosomes to sensitive cells mediating drug resistance.[21] Mitochondrial metabolism plays a central role in cellular energy metabolism where it may have a role in drug resistance by changing the dynamics, which may help to promote drug resistance in various cancers. A study showed that PGC-1α, a principal regulator of mitochondrial biogenesis and energy metabolism, appears to be increased by reprogramming OXPHOS in cisplatin-induced drug-resistant NSCLC and colorectal cancer. It was hypothesized that PGC-1α is a sole regulator of exosome biogenesis in skeletal muscles.[22] PGC-1α can be transported via exosomes to nearby cells altering energy metabolism and promoting drug resistance in lung cancer.

A new investigation revealed that Fyn-related kinase (FRK) plays an oncogenic role by enhancing stemness and metabolic reprogramming in lung cancer, which could be transported via exosomes to drug-sensitive cells.[23] Recent evidence indicates that glycogen branching enzyme (GBE1), a downstream regulator of the hypoxia-inducible factor-1 (HIF1) signaling pathway, induces metabolic changes under hypoxia in *in vitro* as well as *in vivo* conditions.[24] There might be a role of exosomes in transporting GBE1 enzymes participating in the mechanism of metabolic reprogramming, which further needs to be investigated. Also some research shows that cancer-associated fibroblasts (CAFs) deliver snail protein through exosomes, which regulates the hypoxic tumor microenvironment by overexpressing HIF-1α, that leads to drug resistance.[25] There have been reports suggesting that exosomes carrying ALDOA and ALDH3A1 act as signaling factors for the neighboring cells, which can be important for promoting

glycolytic activity and motility in recipient cells.[26] Furthermore, exosomes derived from lung cancer cells were found to express TRIM59, which can be transferred to macrophages via exosomes, activating macrophages, and promotes the progression of lung cancer both *in vitro* and *in vivo,* promoting drug resistance.[27] This evidence suggests that metabolic reprogramming has a role in lung cancer drug resistance that is mediated via exosomes in lung cancer. Exosomes may contribute to the resistance mechanism by transporting specific enzymes, different metabolites that serve in metabolic reprogramming in lung cancer cells. Exploiting the underlying transporting mechanisms via exosomes in the metabolic reprogramming and TME crosstalk may help to decipher different strategies improving drug resistance in lung cancer.

TME REMODELING AS AN ADAPTIVE STRATEGY: CAN EXOSOMES TRANSFORM THE SURROUNDING NICHE?

The TME consists of heterogeneous cell population consisting of CAFs, endothelial cells, immune cells, stem cells, adipocytes, and altered extracellular matrix architecture. These players have a critical role in modulating cancer cells toward invasion and progression ultimately leading to drug resistance. CAFs play a vital role in producing extracellular matrix adaptation to the TME; also growth factors, metabolites via exosomes that can remodel the microenvironment leading to drug resistance in lung cancer.[28] Ke Xu et al. reported that a higher level of Annexin A3 expression shown in CAFs than normal fibroblasts in cisplatin-resistant cells plays an important role in metastasis and drug resistance and Annexin A3 may be transported via exosomes from drug-resistant cells to sensitive cells promoting drug resistance.[29] One group investigated that vascular cell adhesion molecule-1 (VCAM-1), secreted from CAFs, tends to be expressed higher by regulating AKT and MAPK signaling via receptor α4β in lung cancer cells possibly via exosomes.[30] Exosomes released by cancer cells can carry immunosuppressive molecules, such as programmed death-ligand 1 (PD-L1), TGF-β, and interleukin (IL)-10 that can promote an immunosuppressive TME by inhibiting the activation and function of immune cells via exosomes contributing to TME remodeling and resistance mechanisms.[31]

There is certain evidence showing growth factors like vascular endothelial growth factor (VEGF) can also play a part in suppressing the TME. Overexpression of VEGF may promote myeloid-derived suppressor cell (MDSC) infiltration decreasing T cell infiltration and remodeling the TME via exosomes.[32] In addition, it was shown that Hif-1α and Hif-2α are upregulated in cisplatin-resistant lung cancer cells by promoting hypoxia, which further increased BNIP3 and BNIP3L expression safeguarding the cells from cell death.[33] Exosomes derived from NSCLC may contain inflammatory mediators, such as cytokines, chemokines, and growth factors like VEGF, Hif-1α, and Hif-2α that can induce an inflammatory response in the TME, recruiting immune cells and promoting a proinflammatory state.[34] There is new emerging research surfacing, where exosomes can be used as a nanocarrier to deliver various molecules remodeling the microenvironment in NSCLC promoting drug resistance. Also shedding light on different molecules transported across the TME via exosomes may allow scientists to reinforce a novel therapeutic approach and elucidate key pathways in drug resistance.

DRUG TRANSPORTERS IN INCREASED DRUG EFFLUX AND DECREASED DRUG UPTAKE: CAN EXOSOMES ACT AS A MOLECULAR PLAYER?

Increased drug efflux and decreased drug uptake are two mechanisms commonly associated with drug resistance in all the cancer cells as well as bacterial multidrug resistance (MDR). These mechanisms contribute to the reduced effectiveness of multiple drugs and develop resistant strains that worsen the treatment options.

Drug efflux pumps are generally ATP-dependent transporters that actively pump drugs out of the cell, reducing their intracellular concentration. By removing drugs from the cell, efflux pumps can minimize their interaction with the target molecule, leading to reduced drug efficacy leading to drug resistance. Some efflux pump families implicated in drug resistance include ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp), and multidrug resistance-associated proteins.[35] For example, MDR1 is a well-known drug transporter that effluxes chemotherapeutic agents out of cancer cells, leading to drug resistance. MDR1 as well as P-gp can be transported via exosomes and deliver them to lung cancer cells promoting drug resistance.[36] Moreover, ABCG2 has emerged as a key player in drug resistance across different cancer types, including lung cancer. The expression of ABCG2 has been detected in both NSCLC and SCLC subtypes. Elevated levels of ABCG2 expression supposedly transported via exosomes, are frequently linked to resistance against multiple chemotherapeutic drugs commonly employed in lung cancer treatment. Exosomes loaded with ABCG2 inhibitors or modulators can disrupt ABCG2-mediated drug efflux in cancer cells, increasing the intracellular drug concentration and overcoming resistance to chemotherapy.[37] A group of researchers demonstrated that M3814, which is a DNA-PK inhibitor can modulate the function of ABCG2 and overcome ABCG2-mediated MDR, where ABCG2 proteins are found in higher concentrations in exosomes.[38] Moreover, exosomes play a vital role in transferring information from tumor cells to immune and stromal cells within the microenvironment niche. Additional investigations may uncover how different exosomes might play a role in transporting crucial factors related to drug efflux and influx, which would confirm the mechanisms behind drug resistance by the exosomal route in lung cancer.

APOPTOSIS EVASION: CAN EXOSOMES INTERFERE IN THIS TRADITIONAL MECHANISM?

Apoptosis evasion plays a significant role in the development of drug resistance in lung cancer. However, cancer cells often acquire the ability to evade apoptosis, allowing them to survive and continue proliferating even in the presence of anticancer drugs. Apart from that, exosomes are in the limelight for the transportation of various anti-apoptotic factors between drug-resistant cells to drug-sensitive cells promoting drug resistance in lung cancer.

There have been some reports that survivin is secreted via exosomes inhibiting apoptosis and promoting growth in lung cancer cells leading to therapy resistance.[39] In addition, X-linked inhibitor of apoptosis protein (XIAP), a potent inhibitor of apoptosis, was found to be carried by exosomes and delivered to recipient cells, where it inhibits apoptosis and promotes cell survival.[40] Moreover, insulin-like growth factor 1 (IGF-1) has been implicated in promoting cell survival and inhibiting apoptosis in lung cancer. Exosomes derived from lung cancer cells can transport IGF-1 and deliver it to recipient cells activating pro-survival signaling pathways contributing to tumor progression and drug resistance.[41] In a study, it was demonstrated that miR-103a-3p, secreted by CAFs, plays a role in suppressing apoptosis and promoting cisplatin resistance in NSCLC.[42] Experimental evidence confirmed that miR-103a-3p is highly expressed in both CAFs and CAF-derived exosomes in NSCLC. Furthermore, it was observed that miR-103a-3p inhibited apoptosis by directly targeting BAK1, a pro-apoptotic protein.[42] Similarly, Na Shao et al. showed that exosomal circRNA phosphatidylinositol-4-phosphate 5-kinase type 1 alpha (circ_PIP5K1A) from NSCLC helps in regulating progression and cisplatin sensitivity by regulating the miR-101/ABCC1 axis showing that exosomes may act as mediators in transporting circ_PIP5K1A.[43] Also, exosomal FOXD3-AS1 upregulated ELAVL1 expression activating the PI3K/Akt pathway to promote lung cancer proliferation, invasion, and progression as well as 5-FU resistance bypassing apoptotic pathways.[44] A recent publication revealed that exosome-derived NSCLC cells exerted a promoting effect on cell proliferation while inhibiting apoptosis in both normal lung fibroblasts and NSCLC cells. This effect was attributed to the delivery of alpha-smooth muscle actin by exosomes. Specifically, when exosomes isolated from A549 cells were co-cultured with normal lung fibroblast cells (HLFs), an increase in cell proliferation and a decrease in apoptosis were observed.[45] Future research focusing on exosomes and their role in apoptotic evasion in lung cancer drug resistance holds great potential for enhancing our comprehension of this intricate process. By delving into the intricate interplay between exosomes and apoptotic pathways scientists may shed light on previously unknown drug resistance mechanisms to anticancer medications, which may help in cellular phenotypic transitions.

EMT: CAN EXOSOMES INTERPLAY IN THIS AGGRESSIVE PATHWAY?

EMT is a remarkably conserved phenomenon distinguished by the conversion of epithelial cells into mesenchymal cells. EMT is associated with various aspects of tumor biology, including metastasis, drug resistance, and overall tumor advancement. The molecular mechanisms underlying the process of EMT involve the activation of key transcription factors, including SNAIL, Slug, zinc-finger E-box-binding (ZEB), and certain basic-helix-loop-helix transcription factors. The reprogramming of gene expression during EMT is initiated and regulated by various signaling pathways that respond to extracellular signals. Notably, the NOTCH pathway, ERK pathway, PI3K/AKT pathway, and HIPPO pathway play prominent roles in orchestrating this cellular transition, while TGF-β signaling has a predominant role in lung cancer progression.[46]

A study conducted by Xiaoyin Zhao et al. demonstrated that exosomes derived from mesenchymal stem cells (MSCs) promote EMT, invasion, and progression of A549 lung cancer cells activating multiple signaling pathways. Interestingly, when TGF-β1 expression in MSCs was silenced, it resulted in the deactivation of both Smad-dependent and independent pathways that were activated by MSC-derived exosomes.[47] Additionally, when the expression of TGF-β1 was silenced in MSCs, it not only reversed the EMT-promoting effect but also enhanced the anti-proliferative and pro-apoptotic effects of MSCs on lung cancer cells through the delivery of MSC-derived exosomes showing that there might be a role of exosomes transporting TGF-β1 in NSCLC.[48] Subsequent investigations revealed that MSC-derived exosomes activated several key signaling pathways, including Smad2/3, Akt/GSK-3β/β-catenin, NF-κB, ERK, JNK, and p38 MAPK, within the TGF-β1 signaling pathway in lung cancer cells. Conversely, silencing TGF-β1 expression in MSCs resulted in the deactivation of these pathways, thereby suggesting their dependency on TGF-β1 for activation in the context of MSC-exosome-mediated effects.[49] Moreover, the levels of Snail-1 in exosomes released by CAFs were found to be correlated with the induction of EMT in NSCLC. Notably, when CAFs were treated with GW4869, an inhibitor of exosome release, it effectively inhibited their ability to induce EMT in recipient cells.[50] A study demonstrated that there was a significant upregulation of CircFARSA in NSCLC cells. Moreover, the overexpression of CircFARSA was found to enhance the metastatic potential of NSCLC.[51] However, when NSCLC cells were co-cultured with macrophages transfected with circFARSA, it resulted in enhanced EMT and metastasis. The underlying mechanism involving exosomal circFARSA that induces M2 polarization through PTEN ubiquitination and degradation, subsequently activates the PI3K/AKT signaling pathway.[52] These findings highlight the role of exosomal circFARSA in promoting NSCLC progression by modulating macrophage polarization and activating key signaling pathways. Multiple research studies have shown the importance of exosomes from CAFs and MSCs in promoting EMT, invasion, and progression and developing drug resistance. More research is needed to explore the underlying mechanisms of how exosomes support in assisting the normal cells to switch their phenotypic character during EMT and MET, escaping different therapeutic strategies promoting drug resistance in lung cancer (Figure 1).

TRANSPORT OF DIFFERENT FACTORS PROMOTING DRUG RESISTANCE IN LUNG CANCER VIA EXOSOMES

Protein factors transport

There are various kinds of proteins that are transported via exosomes and regulate intracellular communication, signaling, and several other mechanisms leading to drug resistance in cancer as previously discussed. For example, CD44 and integrins, involved in cell adhesion, can be carried to recipient cells via exosomes to nearby cells in the TME.[53] Cancer cells with enhanced DNA repair capabilities are often resistant to DNA-damaging agents, such as chemotherapy or radiation therapy. Exosomes released by DNA repair-proficient

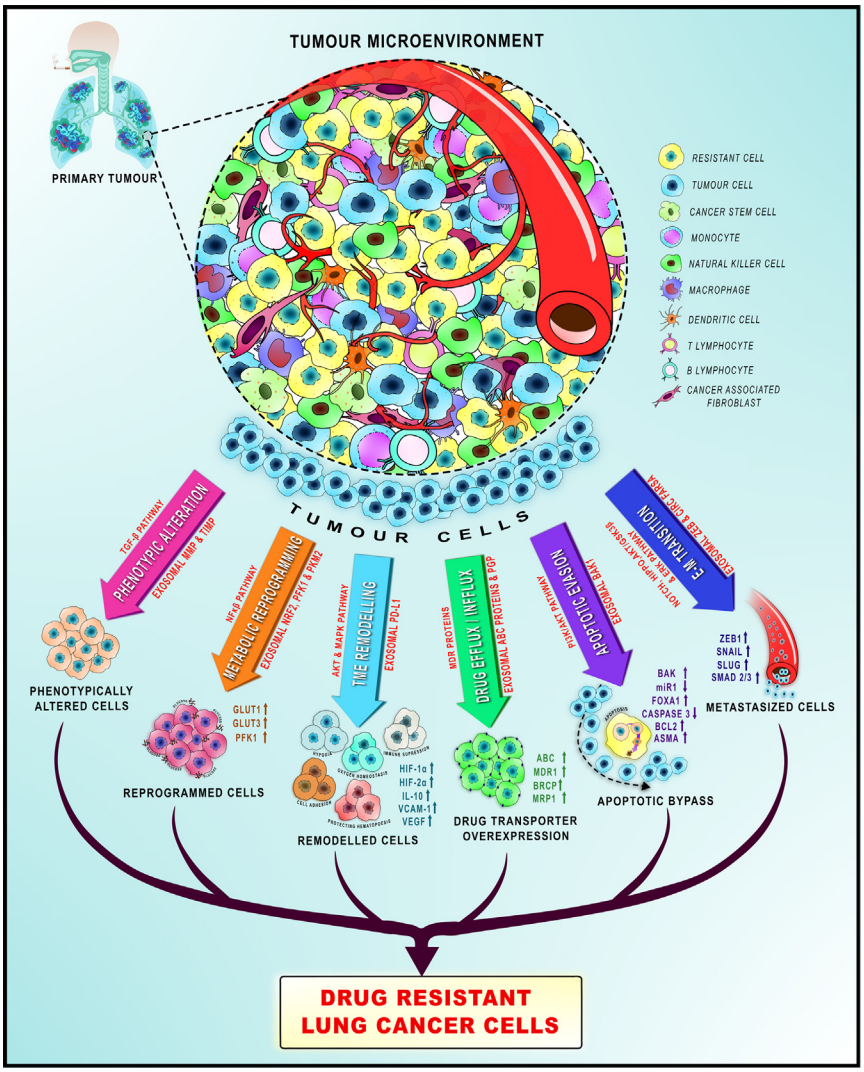

Figure 1. The role of exosomes in modulating drug resistance mechanisms in lung cancer

This figure illustrates the potential roles of exosomes in modulating various drug resistance mechanisms in lung cancer. The drug-sensitive cancer cells are transformed into resistant cells by changing their morphology and forming heterogeneous types of cells where exosomes play a critical role in changing the phenotypes. Also, exosomes may help in rewriting the recipient cells by delivering drug transporters, anti-apoptotic factors, or transferring survival signals, EMT-inducing factors, signaling molecules, or genetic material, promoting drug resistance in lung cancer cells.

cancer cells can transfer DNA repair proteins, such as RAD51, O6-methylguanine-DNA methyltransferase (MGMT), or DNA-PK, to neighboring cells enhancing their DNA repair capacity and conferring resistance to DNA-damaging treatments conferring therapeutic resistance and relapse mechanisms.[54,55] Increased expression of DNA repair proteins enhances the capacity of recipient cells to repair DNA damage induced by chemotherapy or radiation therapy, leading to drug resistance. In addition, EGFR is a receptor tyrosine kinase that plays a role in cell growth and survival. Overexpression or mutation of EGFR is associated with resistance to targeted therapies, such as EGFR-TKIs, in certain cancers as well as lung cancer. Exosomes derived from EGFR-driven resistant cancer cells can transfer EGFR and its mutant variants to recipient cells.[56] This transfer can lead to activation of downstream signaling pathways, circumventing the inhibitory effects of targeted therapies. Emerging research is going on to unveil the underlying mechanisms of exosomal protein transport in multiple cancers including lung cancer. Thorough investigations are needed to establish the mechanisms of involvement of exosomes in transporting various protein factors in developing drug resistance in lung cancer (Table 1).

Anti-apoptotic factors transport

Anti-apoptotic factors are a group of cellular constituents that inhibit the apoptotic process, promoting cell survival. These factors can protect cells from apoptosis by preventing the activation of apoptotic pathways, inhibiting the release of pro-apoptotic factors, or promoting cell survival signals. While the transport of apoptotic factors is a well-documented process, the transfer through exosomes is a relatively less explored area of research. Several studies have shown that exosomes derived from cells expressing anti-apoptotic proteins can transfer these proteins to recipient cells, influencing their apoptotic susceptibility. For example, exosomes derived from cancer cells that overexpress anti-apoptotic proteins such as Bcl-2 or survivin have been found to confer resistance to apoptosis in recipient cells in breast cancer.[57] In hematological malignant cells, caspase-3 cleaved Bcl-xL is shown to be transferred via exosomes and uptake by recipient cells.[58] Exosomal survivin also was shown to be an activator of TME promoting lung cancer and evading apoptosis.[39] Another anti-apoptotic protein, XIAP was found to be carried by exosomes in prostate cancer restraining apoptosis and promoting metastasis, which might have a role in drug resistance in lung cancer.[59] Heat shock proteins (HSPs) encompass a cluster of molecular chaperones that play a crucial role in shielding cells against various forms of stress while bolstering cellular viability. Certain HSPs, such as Hsp70 and Hsp90, have been identified as markers in exosomes. These exosomal HSPs can be taken up by recipient cells, where they may confer cytoprotective effects by inhibiting apoptotic pathways and promoting cell survival.[60] Akt, also known as protein kinase B, is a key signaling molecule involved in promoting cell survival and inhibiting apoptosis. Activated Akt has been detected in some exosomes and can be delivered to recipient cells.[61] Once inside

Table 1. Exosomal factors responsible for drug resistance in lung cancer and their functions

Types of exosomal factor	Exosomal factors	Functions	Expression level	Reference
Proteins	YAP1	Regulation of cell proliferation and apoptosis, drug resistance.	Upregulated	Song et al.[89]
	c-Src	Signaling pathways related to cancer progression and drug resistance.	Upregulated	Clark et al.[90]
	CD44	Promotes cancer stemness, enhances drug resistance.	Upregulated	Szatanek, R. and M. Baj-Krzyworzeka[91]
	FasL	Immune regulation, apoptosis resistance, enhance resistance to chemotherapy.	Upregulated	Cai et al.[92]
	PD-L1	Inhibits immune cell activation, proliferation, and survival and cytotoxic secretion within cancer cell.	Upregulated	Kim et al.[93]
	ERCC1	DNA repair enzyme involved in nucleotide excision repair.	Upregulated	Ridder et al.[94]
	COX2	Facilitates tumor cell proliferation, invasion, metastasis, angiogenesis, and confers resistance to anticancer therapies.	Upregulated	Kim et al.[95]
	SDF1	Mediates chemotaxis, migration, and secretion of angiopoietic factors.	Upregulated	Wang et al.[96]
Lipids	Sphingomyelin	Regulates cell survival, modulates drug response.	Upregulated	Tallima et al.[97]
	Ceramide	Induces apoptosis, modulates drug response.	Upregulated	Hsu et al.[98]
	Cholesterol	Modulates membrane fluidity, affects drug response.	Upregulated	Hsu et al.[98]
	Phosphatidylserine	Regulates cell signaling, affects drug response.	Upregulated	Xia et al.[99]
	Phosphatidylethanolamine	proliferation, differentiation, metastasis and therapy resistance of tumors.	Upregulated	Hsu et al.[98]
RNAs	miR-126	Enhances drug resistance, promotes angiogenesis.	Upregulated	Chen et al.[100]
	miR-125b	Enhances resistance to docetaxel and cisplatin by targeting BAK1 and Bcl-2, inhibiting apoptosis, and promoting cell survival.	Upregulated	Zhang et al.[101]
	miR-17-92	Confers resistance to cisplatin and paclitaxel by targeting PTEN and BIM, promoting cell survival, and inhibiting apoptosis.	Upregulated	Yang et al.[102]
	miR-34a	Suppresses resistance to cisplatin and doxorubicin by targeting Bcl-2 and Notch1, promoting apoptosis, and inhibiting cell proliferation.	Downregulated	Wu et al.[103]
	miR-146a	Mediates resistance to EGFR inhibitors by targeting EGFR itself, activating the NF-κB pathway, and promoting cell survival and proliferation.	Upregulated	Wani et al.[104]
	miR-99a	Contributes to resistance to cisplatin and gefitinib by targeting mTOR, activating the PI3K/Akt pathway, and promoting cell survival and proliferation.	Upregulated	Akbarzadeh et al.[105]
	miR-10b	Contributes to resistance against various chemotherapeutic agents by targeting HOXD10, promoting cell survival, and inhibiting apoptosis.	Upregulated	Iswariya et al.[106]
	H19 (LncRNA)	Induction of EMT, activation of oncogenic signaling pathways, and changes in the tumor microenvironment.	Upregulated	Pan, R. and H. Zhou[107]

the recipient cells, exosomal Akt can activate downstream signaling pathways that promote cell survival and inhibit apoptosis.[38] Certain miRNAs with anti-apoptotic functions, such as miR-21 and miR-29a, also have been found to be transported via exosomes.[62] These miRNAs can be transported to recipient cells targeting pro-apoptotic genes, promoting cell survival and drug resistance. Ongoing research must continue to identify additional anti-apoptotic factors transported via exosomes and their involvement in pathway modulation and drug resistance in lung cancer.

Transport of transcription factors

While the primary role of exosomes is to transport various biomolecules, such as proteins, lipids, and nucleic acids, the transport of transcription factors via exosomes is still an area of ongoing research and is not fully understood yet. Although the transport of transcription factors through exosomes has not been extensively characterized, there is emerging evidence suggesting that certain transcription factors are found in exosomes. Twist1, a transcription factor involved in EMT, can be packaged into exosomes derived from cancer cells and may induce EMT in recipient cells, leading to increased invasion and metastasis in lung cancer.[63] Likewise, STAT5 and STAT3 have been observed to be transferred via exosomes between immune cells, such as regulatory T cells and dendritic cells. Exosomal STAT5 can be transferred to recipient cells to influence immune responses and regulate gene expression.[64] A recent study showed that Runx1 (known as AML1), a transcription factor that plays a critical role in hematopoiesis and leukemia, can be transported via exosomes derived from leukemia cells.[65] Exosomal transfer of HIF-1α has been proposed as a mechanism for intercellular communication and modulation of cellular responses to hypoxia, where some reports suggest that HIF-1α can be transported via exosomes.[66] In addition, LMP1, a transcription factor, plays a crucial role in promoting the growth, survival, EMT, angiogenesis, and metastasis of cancer cells by modulating the stromal cells within the TME. Some reports have found that LMP1 can be transported via exosomes.[67,68] YAP and TAZ are transcriptional coactivators that play a crucial role in the Hippo signaling pathway, responsible for regulating cell proliferation and organ size. Interestingly, these factors have been identified in exosomes derived from lung cancer cells. The presence of YAP and TAZ in these exosomes can significantly impact the behavior of recipient cells, ultimately promoting tumor growth and metastasis and drug resistance.[69] Further research is needed to fully elucidate the extent and functional implications of transcription factor transport via exosomes in lung cancer. The understanding of transcription factor transport via exosomes is in its early stages; these initial findings suggest that exosomes may have a role in the intercellular transfer of transcription factors, potentially influencing drug resistance mechanisms in lung cancer.

EMT factors transport

EMT factors are transcription factors and other molecules that regulate the transition of epithelial cells into a mesenchymal phenotype, characterized by increased migratory and invasive properties. For example, Snail is shown to be packaged into exosomes and transferred to neighboring or distant cells promoting drug resistance in NSCLC.[70] Exosomal Snail can trigger EMT and enhance cancer cell invasiveness. Also Slug, closely related to Snail, regulates EMT by modulating the expression of genes involved in cell adhesion and migration. Exosomal transfer of Slug may be possible in NSCLC, and it can promote EMT-related changes in recipient cells. Some research shows that zinc-finger E-box-binding Homeobox 1 (ZEB1) and ZEB2 are transcription factors that are critical regulators of EMT. Both ZEB1 and ZEB2 mRNA have been detected in exosomes derived from cancer cells.[71] Exosomes derived from lung cancer cells have been found to carry E-Cadherin, suggesting a potential mechanism for the removal or sequestration of E-Cadherin from cancer cells. This transfer of E-Cadherin via exosomes can contribute to the loss of cell-cell adhesion and promote the invasive behavior of recipient cells.[72] Moreover, certain integrins, such as αvβ6 and α6β4, have been identified in exosomes derived from lung cancer cells.[73] The transfer of integrins via exosomes can modulate cell-matrix interactions and contribute to the migratory and invasive behavior of recipient cells, which can develop therapy resistance in lung cancer cells.

Further research must continue to unravel the role of various EMT factors involved with exosomes in lung cancer progression and therapy resistance mechanisms.

Angiogenesis factors transport

Angiogenesis is a critical process in various physiological and pathological conditions, including cancer. Several angiogenesis factors have been identified to be transported via exosomes.[74] Angiogenesis factors such as VEGF, one of the most well-known angiogenesis factors, have been found to carry VEGF in cancer cells, including lung cancer. Fibroblast growth factor (FGF) is another potent angiogenesis factor that promotes endothelial cell proliferation and migration. It has been detected in exosomes derived from cancer cells. Exosomal FGF can induce angiogenic responses in recipient cells and facilitate the formation of new blood vessels.[75] Angiogenin is a protein involved in promoting angiogenesis. Exosomes derived from glioblastoma cells contains seven angiogenin proteins.[74] These proteins stimulate endothelial cell proliferation and migration, leading to the formation of newer blood vessels. There might be a possibility that exosomes derived from lung cancer cells carry angiogenin, which may unravel newer avenues in lung cancer research involving angiogenic factors. Some cytokines like IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α are proinflammatory cytokines that can also act as a potent angiogenic factor. Exosomes derived from lung cancer and colon cancer cells have been shown to carry IL-8. The transfer of exosomal IL-8 can stimulate angiogenesis and contribute to tumor vascularization.[76] Likewise, other proinflammatory cytokines can be carried by exosomes creating an inflammatory environment supporting the growth of tumor. In addition, TSP-1 is a matricellular protein with both anti-angiogenic and pro-angiogenic properties and is shown to be carried via exosomes derived in breast cancer cells.[77] The transfer of exosomal TSP-1 can influence endothelial cell behavior and modulate angiogenesis in recipient cells.[78] TSP-1 may be transported via

exosomes and may promote angiogenesis in lung cancer, which is not yet reported and holds a great promise in therapeutic drug resistance research. Some angiogenesis factors, as discussed above, have been reported to be transported via exosomes in different types of cancer as well as lung cancer. Besides that, lung cancer-derived exosomes carrying angiogenesis factors have not been explored yet. Ongoing research must continue to uncover additional angiogenesis factors and shed light on their roles in exosome-mediated drug resistance in lung cancer.

Lipid factors transport

Lipids play crucial roles in cellular functions, including membrane structure, energy storage, and signaling. Recent research shows exosomes have been implicated in the transport of lipids such as cholesterol, fatty acids, and eicosanoids in various cellular processes, including cancer.[79] During the formation of exosomes, lipid molecules can be selectively sorted and incorporated into the exosomal membrane and transported to the neighboring cells.[80] However, cancer cells release exosomes that contain unique lipid signatures. These lipid signatures can differ from those of normal cells and may reflect the metabolic alterations and pathological state of the cancer cells.[81] The transfer of these lipids via exosomes in cancer can have functional implications for cancer progression and resistance. These lipids transferred via exosomes can serve as signaling molecules in recipient cells. For instance, lipid molecules like lysophosphatidic acid or sphingosine-1-phosphate (S1P) carried by exosomes can activate signaling pathways associated with cancer cell survival, migration, and metastasis.[82] Also, cholesterol-rich exosomes can be released by cancer cells and taken up by recipient cells, contributing to altered cholesterol homeostasis and promoting tumorigenesis.[83] Moreover, exosomes can transfer specific lipids and lipid-associated enzymes that can reprogram recipient cells' lipid metabolism, supporting the unique lipid requirements of cancer cells.[83] Additionally, fatty acids such as palmitic acid and oleic acid, can be carried by exosomes. These fatty acids can affect cellular signaling pathways, including inflammation, lipid metabolism, and cancer progression.[84] Numerous studies have proved that lipids may play a vital role in cancer invasion and progression pathways in different types of cancer; there are a few studies showing that lipids are carried and transported by exosomes to neighboring cells and transform them into resistant cells. Exploring the roles of lipids transported via exosomes may open new possibilities of research for the treatment of drug resistance in lung cancer (Table 1).

miRNA transport

The transport of microRNAs (miRNAs) via exosomes is an active area of research and well-established. Exosomes serve as vehicles for intercellular communication, and they can transfer miRNAs between cells, influencing gene expression, various cellular processes in cancer. During the biogenesis of exosomes, specific miRNAs can be selectively incorporated into the exosomes and this packaging is mediated by interactions between miRNAs and RNA-binding proteins, such as the RNA-induced silencing complex, which plays a role in miRNA loading into exosomes.[62] Similarly, miR-21 is one of the most well-studied miRNAs in exosomes. It is often upregulated in cancer and has been found to be transferred from cancer cells to recipient cells via exosomes. Exosomal miR-21 has been associated with promoting tumor growth, invasion, metastasis by targeting various tumor suppressor genes, and most importantly is involved in therapy resistance.[85] Additionally, mir-155 is an important miRNA involved in immune responses and inflammatory processes. It has been detected in exosomes derived from immune cells, such as B cells and dendritic cells. Exosomal miR-155 can be transported to recipient cells, modulating gene expression and immune responses.[86] Moreover, the let-7 miRNA family plays a crucial role in developmental processes and is often dysregulated in cancer.[87] Also, exosomal miR-1246, miR-146a, and miR-29 are found in different cancers, which are involved in tumor progression, drug resistance, and metastasis.[88] The transfer of miRNAs via exosomes provides a mechanism for cells to communicate and influence gene expression in recipient cells, shaping various cellular processes and disease outcomes. These examples signify the diverse roles of miRNAs transported via exosomes in lung cancer. Targeting these domains will uncover new realms underlying miRNA and lung cancer crosstalk intervening in lung cancer drug resistance (Figure 2; Table 1).

PROGRESSION AND MAINTENANCE OF DRUG RESISTANCE BY EXOSOMAL FACTORS IN LUNG CANCER

As this extensive review suggests, exosomal factors may play a crucial role in the progression of drug resistance in lung cancer by transporting bioactive molecules between cancer cells. These exosomes may contribute to drug resistance by transmitting resistance-conferring molecules, activating survival pathways, and enhancing TME remodeling. Exosomal cargo can foster cellular adaptations, such as enhanced DNA repair and altered drug efflux mechanisms, ultimately promoting treatment evasion and tumor growth. Also, these exosomal factors might have a role in maintaining drug resistance capacity by autocrine or paracrine signaling in lung cancer cells for a prolonged period of time supporting the cells to maintain resistant phenotypes.[108] In addition, exosomes may have a conflicting role in suppressing the TME, promoting apoptosis. For example, M1-macrophage-derived exosomes (M1-exos) can inhibit tumor progression by enhancing immune response and promoting apoptosis. These M1-exos can carry miR-181a-5p to target ETS1, inhibiting the expression of STK16 (Serine/threonine kinase-16) in tumor cells.[109] Likewise, M1-exos can carry miR-16-5p, exerting an inhibitory effect on gastric cancer progression via PD-L1 activating T cell immune response.[110] Similarly, exosomes from other immune cells such as NK cells, dendritic cells, B cells, Mast cells, and neutrophils have direct anti-tumor activity having a positive effect.[111] There is no compelling evidence for this least explored area between exosomes and cancer, more specifically lung cancer, and how their crosstalk helps to maintain the phenotypic characteristics and microenvironment of resistant cells.

THE INTERPLAY BETWEEN EXOSOMES AND DRUG RESISTANCE IN LUNG CANCER

From the above literature review it can be concluded that exosomes may play a significant role in intercellular communication by

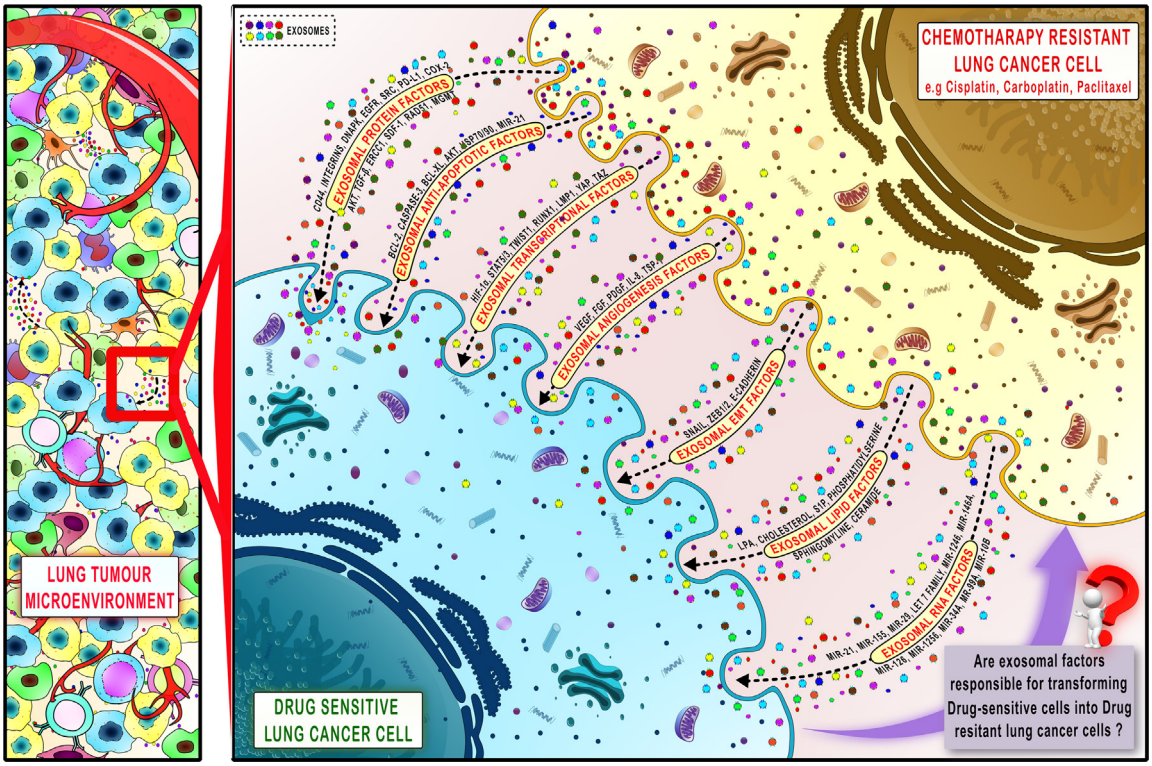

Figure 2. Transport of various exosomal factors from chemotherapy drug-resistant cells to drug-sensitive cells in lung cancer

The figure highlights the role of exosomes in transporting various factors such as protein factors, lipid factors, RNAs, anti-apoptotic factors, transcription factors, and epithelial-mesenchymal factors promoting drug resistance in lung cancer.

transferring bioactive molecules from donor cells to recipient cells. In the context of cancer, exosomes have been implicated in tumor progression, metastasis, and drug resistance. While the mechanisms underlying drug resistance in lung cancer are multifactorial, exosomes may have a role in the development of resistance by facilitating communication between cancer cells. Additionally, exosomes may influence the TME by modulating the behavior of surrounding cells. For example, some anti-apoptotic molecules, EMT factors, and angiogenesis factors can be transferred and modulate the TME, so the altered microenvironment can contribute to the development of drug resistance by providing a supportive niche for drug-resistant cancer cells. Understanding the mechanisms by which exosomes contribute to drug resistance can potentially lead to the development of novel therapeutic strategies to overcome resistance and improve the outcomes for lung cancer patients.

CLINICAL ASPECTS OF EXOSOMES

Exosomes contain a variety of biomolecules that reflect the composition of their parent cell and travel through the bloodstream and other body fluids to interact with distant cells and modulate their functions. These nanovesicles can be engineered to deliver specific cargos and used as drug delivery agents and targeted therapy. Due to biocompatibility and lower immunogenicity than other drug delivery systems, these bioengineered exosomes can be the future of drug delivery systems to some larger extent. These bioengineered nanovesicles can cross the lipid bilayer and blood-brain barrier easily and target specific molecules on the cancer cells allowing more precise delivery of therapies and reduced side effects on healthy tissues,[112] so it will be advantageous to target cells that are different from other traditional therapies. Apart from drug delivery, exosomes can also be used for biomarker studies, vaccine development, and gene therapies as well. These vesicles are currently being explored for a wide range of clinical applications, including cancer immunotherapy, neurological disorders, cardiovascular disease, etc. A survey on Clinicaltrials.gov (https://clinicaltrials.gov/) displays the major applications of exosomes including biomarker study, exosome therapy, drug delivery systems, and cancer vaccines. There are more than 100 trials done involving exosomes, from which 50% belong to exosome biomarker applications, 30% belong to exosome therapy, 10% belong to drug delivery systems, and 15% belong to basic analysis of exosomes.[113] For example, a clinical trial was conducted to explore the ability of grape plant exosomes to prevent oral mucositis, which is associated with chemoradiation treatment of head and neck cancer (NCT01668849).[113] Also, many other articles published compilations of exosome use in pre-clinical and clinical trials.[114–118]

In addition to that, high-throughput screening identifies selective inhibitors and activators of exosome biogenesis such as tipifarnib,

climbazole, triadimenol, sitafloxacin, nitrefazole, and pentetrazol, which can be potentially utilized as novel therapeutic options in advanced cancers. By exploring the underlying mechanisms of delivery systems of exosomes and targeting exosome biogenesis, new therapeutic avenues will be established for the betterment of personalized cancer treatment.

DISCUSSION AND CONCLUSIONS

Exosomes have emerged as key mediators of drug resistance in lung cancer, offering new avenues for understanding and addressing this major clinical challenge. They play a significant role in promoting drug resistance in cancer, and the future in this area of research holds great promise. By transferring specific mRNAs, ncRNA, miRNA, and proteins, exosomes can induce drug resistance in tumor cells.[119] So, these exosomes can modulate drug resistance via different mechanisms by transporting drug efflux pumps, DNA damage repair proteins, TME acidity, autophagy, dysregulation of oncogenes, and tumor suppressor genes, which is well documented.[55] The field of exosomes research in cancer is rapidly evolving, and there are several exciting directions and potential future developments. By harnessing the potential of exosomes, researchers and clinicians can potentially overcome drug resistance, improve patient outcomes, and advance the field of lung cancer treatment. Understanding precise mechanisms by which exosomes contribute to drug resistance is crucial. Further research efforts should aim to unravel the intricate molecular cargo carried by exosomes, which may play pivotal roles in modulating drug resistance. By elucidating these mechanisms, researchers can identify potential therapeutic targets and develop strategies to disrupt exosome-mediated drug resistance.

Future research efforts will focus on elucidating the complex mechanisms by which exosomes contribute to drug resistance in lung cancer as well as other cancers. A deeper understanding of exosome-mediated drug resistance will facilitate the development of targeted therapeutic strategies.

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AUTHOR CONTRIBUTIONS

S.K.P.: Conceptualization, Formal analysis, Visualization, Writing - original draft; review & editing; R.K.S.: Visualization, designing figures, review & editing; S.B.: Review & editing; S.S.P.: Review & editing; B.K.B.: Conceptualization, Supervision, Writing-review & editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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