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Exosomal long non-coding RNAs in cancer: Interplay, modulation, and therapeutic avenues

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ABSTRACT

In the intricate field of cancer biology, researchers are increasingly intrigued by the emerging role of exosomal long non-coding RNAs (lncRNAs) due to their multifaceted interactions, complex modulation mechanisms, and potential therapeutic applications. These exosomal lncRNAs, carried within extracellular vesicles, play a vital partin tumorigenesis and disease progression by facilitating communication networks between tumor cells and their local microenvironment, making them an ideal candidates for use in a liquid biopsy approach. However, exosomal lncRNAs remain an understudied area, especially in cancer biology. Therefore this review aims to comprehensively explore the dynamic interplay between exosomal lncRNAs and various cellular components, including interactions with tumor-stroma, immune modulation, and drug resistance mechanisms. Understanding the regulatory functions of exosomal lncRNAs in these processes can potentially unveil novel diagnostic markers and therapeutic targets for cancer. Additionally, the emergence of RNA-based therapeutics presents exciting opportunities for targeting exosomal lncRNAs, offering innovative strategies to combat cancer progression and improve treatment outcomes. Thus, this review provides insights into the current understanding of exosomal lncRNAs in cancer biology, highlighting their crucial roles, regulatory mechanisms, and the evolving landscape of therapeutic interventions. Furthermore, we have also discussed the advantage of exosomes as therapeutic carriers of lncRNAs for the development of personalized targeted therapy for cancer patients.

1. Introduction

Exploring exosomal lncRNAs and unveiling their intricate landscape in cancer biology is evolving. Exosomal lncRNAs participate in several processes in tumor development and progression, like cell growth, angiogenesis, metastasis, and immunomodulation. Exosomes are pivotal in cell-to-cell communication in normal physiology and the tumor microenvironment (TME). Exosomes are extracellular vesicles with a 30–50 nm diameter [1], and are released ubiquitously by different body cells. These organelles carry abundant molecules including proteins, nucleic acids and carbohydrates derived from their parent cells to recipient cells, known as exosomes' cargo. This exosome cargo can affect the recipient cells' function and activity [2]. Compared to normal cells, cancer cells together with stromal cells and immune cells in TME are revealed to produce more exosomes to mediate their activity in the TME [3]. This dynamic TME undergoes transitions from pre-tumor to invasive tumor states, with signals transmitted through cytokines, hormones, and growth factors, either by direct contact or through extracellular vesicles (EVs) [2,4–7]. Exosomes were initially described to be primarily useful in cellular waste secretion [8]. However, now they are known for their active participation in cellular communication, physiology and patho-physiology [9–11]. Exosomes have been reported to have decreased immunogenicity. They are capable of crossing the blood brain barrier, owing to their tiny size and membrane composition. The differential

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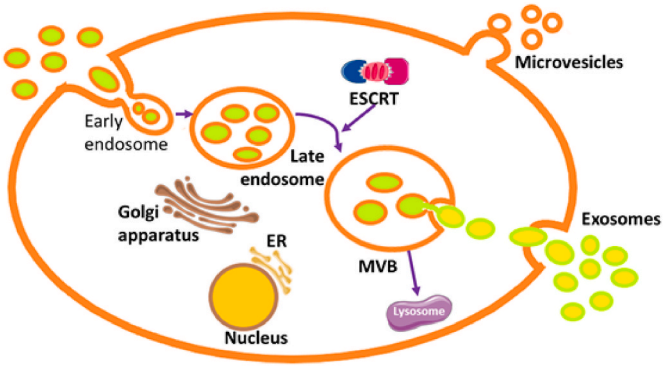

Fig. 1. Biogenesis of exosomes. This process begins by the invagination of the plasma membrane into early endosomes and subsequent invagination of the endosomal membrane resulting in the ILVs/MVBs development. The endosomal sorting complex required for transport (ESCRT) is required to facilitate ILVs/MVBs development, vesicle budding, and sorting o ILVs/MVBs contents. Fusing of the ILVs/MVBs with the plasma membrane results in discharging of exosomes in the extracellular region. Microvesicles result from direct plasma membrane budding.

exosome populations differ in their size, composition and biophysical properties, with exosomal lncRNAs being smaller in size compared to exosomal proteins and this is associated with their physiological or pathological functions [12]. Similarly, lncRNAs and miRNAs can exist in exosomes stably [13–18]. The worth of exosomal lncRNAs in tumor biology is understudied, compared to exosomal miRNAs, and this requires significant efforts from cancer biologists to decipher the associated mechanisms. The spatiotemporal exosomal lncRNA gene expression patterns, roles and precise mechanisms are yet to be fully understood in cancer biology. Hence, this review discusses exosomal lncRNAs as active role players in TME and their mechanisms in tumor progression, metastasis and immunomodulation, as they mediate intercellular communication.

Despite substantial advancements in the diagnosis and management of cancer metastasis in recent years, challenges persist, including a limited number of detection markers, the rapid dissemination of cancer cells, and suboptimal prognoses with low survival rates. While biopsy remains the gold standard for cancer diagnosis, the necessity for early-stage detection and the crucial exploration of the disease's molecular intricacies to guide treatment strategies have stimulated the emergence of alternative diagnostic methods. Among these, liquid biopsy stands out as a promising non-invasive option to aid therapeutic advances in developing personalized cancer medicine for better treatment outcome. Circulating lncRNAs are also being evaluated as liquid biopsybiomarkers in cancers [19,20]. Also, lncRNAs are believed to depict the tumor heterogeneity and harbor the same mutational landscape as the tumor bulk and thus, their fragmentation patterns might contain footprints of the mutational landscape and tissue of origin of the tumor cells. Thus, this review provides insights into the current understanding of exosomal lncRNAs in cancer biology, highlighting their crucial roles, regulatory mechanisms, the evolving landscape of therapeutic interventions and limitations associated with their clinical applications. Additionally, we have also discussed the advantage of exosomes as therapeutic carriers of lncRNAs for the development of personalized targeted therapy for cancer patients.

2. Exosome biogenesis, characterization and biodistribution

2.1. Biogenesis of exosomes

Exosomes are lipid bilayers derived from endosomes and contain a myriadof bioactive molecules including lipids, proteins and nucleic acids [21]. Exosomes are secreted from almost all cell types, including tumor, immune and epithelial cells [22,23]. The early endosomes are changed into the late endosomes by the Golgi complex. The late endosome compartments limiting membranes invaginate further forming intraluminal vesicles (ILVs) and encapsulating cargoes from donor cells. The ILVs assemble into multivesicular bodies (MVBS). While some MVBs can merge with the cytoplasmic membrane, eventually forming EVs, others are degraded by the intracellular lysosomes [24]. Based on the ISEV2018 guidelines, the standard naming of EVs is according to the

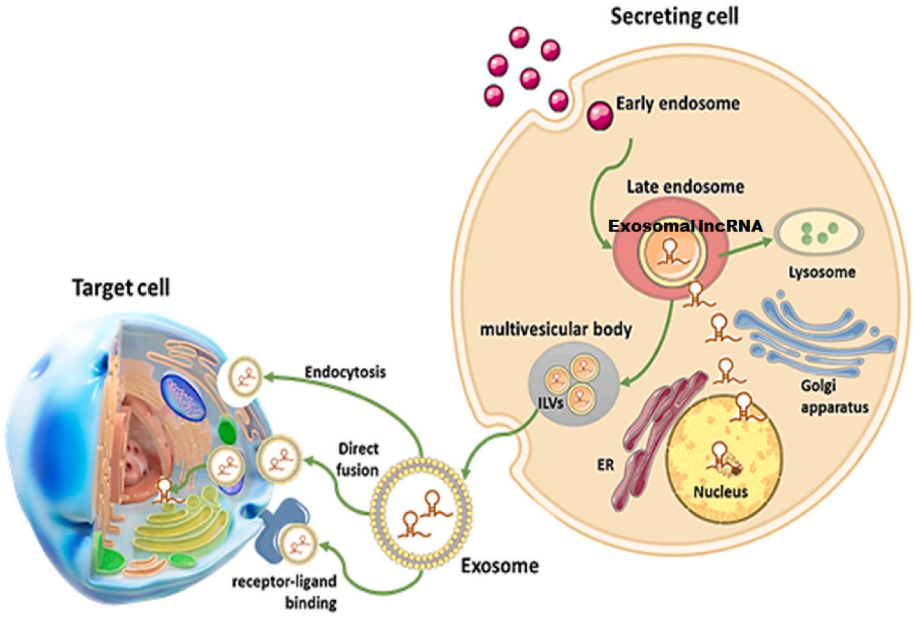

Fig. 2. Illustration of mechanisms of secretion and reception of exosomal lncRNA from the secretor cells to target cells. The process begins with invagination of the plasma membrane resulting in an early endosome released into the cytoplasm. The second invagination produces mature intracellular multivesicular bodies (MVBs) responsible for the organization of the ILVs. Long coding RNA will then be incorporated into the ILVs and ILVs released into the extracellular environment, where they are taken up by the target cells as exosomal lnRNAs through several mechanisms including endocytosis, direct fusion, and receptor-ligand binding. Other MVBs will fuse with the lysosomes for degradation. Upon arrival into the target cells, exosomal lncRNAs release InRNAs into the target cells for various functions in cancer.

biochemical composition, physical characteristics (size and density) and cell origin [25]. Fig. 1 refers to the biogenesis of exosomes.

2.2. Exosome delivery, characterization, biodistribution and intercellular communication

Exosomes facilitate cell-to-cell communication locally and systemically [26]. In addition, exosomes may undergo various cycles of cell uptake to access several tissue layers. In this communication, the origin of the cell, composition of exosome and exosomal administration route, are all critical factors affecting exosome biodistribution. Specific targeting to recipient cells is key to delivering exosomal lncRNAs and exerting their functions [27]. The surface compositions of the exosomes and the receiving cells are essential for this interaction. Exosomes can either trigger intracellular signaling when reaching the target cell or can directly fuse with the plasma membrane. For signal transducing mechanisms, the exosomal transmembrane ligands directly fuse with recipient cells surface receptors [28,29]. However, a wide research gap still exists in this downstream signaling, particularly with the multifaceted nature of the lncRNAs.

Exosomes and their cargo have been reported to be stable in liquid biopsies. Liquid biopsy is a multifaceted strategy in clinical oncology diagnosis. This approach enables clinicians to investigate, identify and monitor malignancies in body fluids including serum, blood, plasma and urine [30]. Exosomal biomarkers have been reported to have improved performance in tumordiagnosis and prognosis compared to the sole use of liquid biopsy [31–33]. Ultracentrifugation and commercial isolation kits are standard techniques for exosomes' extraction, although it has been reported that improvements are still required in exosome purity and isolation studies. Notably, ultracentrifugation provides pure exosomes but with low isolation efficiency. On the other hand, commercial kits have very high efficiency but accompanied by low purity [34,35]. Exosomes have been reported to be more stable with increased concentrations in body fluids compared to free nucleic acids and circulating tumor cells [36,37]. Fig. 2 illustrates mechanisms of reception of exosomal lncRNA from the secretor cells [38].

3. Exosomal lncRNAs in tumor biology

3.1. Exosomal lncRNAs in tumor invasion, angiogenesis and metastasis

Exosomal lncRNAs play a significant role in tumor metastasis, shown to alter the expression of cancer signaling pathways. It has been discovered that exosomal lncRNAs function as competing endogenous RNAs (ceRNAs) and sponge miRNAs, thereby regulating target gene expression. They can also bind target proteins, affecting their ubiquitination and phosphorylation, thus modulating their expression and activity. This, in turn, affects signaling pathways related to tumor metastasis. However, exosomal lncRNAs mechanisms in tumor metastasis remains largely to be elucidated as there is a broad range of intra-and-intercellular downstream targets [38].

As cancer cells shed off from the primary site, they also shed off their contents, such as lncRNAs. These lncRNAs may be encapsulated by exosomes. The exosomal lipid bilayer protects exosomal contents from proteases and RNAses, rendering them valuable molecules in translational oncology [39]. For instance, exosomal lncRNA TERC was discovered to be considerably higher in bladder cancer patients' urinary exosomes with increased sensitivity (78.65%) and accuracy (77.78%). Similarly, tumor-derived exosomal lncRNAs can stimulate pro-angiogenesis of circulating angiogenic cells. This is achieved by the upregulation of membrane molecules and soluble factors expression [40]. The Tumor angiogenesis process includes the vessel's membrane enzymatic degradation, endothelial cell growth, migration, sprouting, branching, and formation of the tube. During the process of angiogenesis, exosomes produced by various kinds of cells, including stromal cells, mesenchymal stem cells, and endothelial cells are important mediators in the TME [41–46]. Furthermore, exosomal lncRNAs, including lncRNA Sox2ot and RNA-UCA1, are shownto encourage invasion, growth, and migration in pancreatic ductal adenocarcinoma (PDAC) and bladder cancer, respectively [47,48]. Other exosome-encapsulated lncRNAs, including lncRNA PCGEM1, MALAT1, RP11-85G21.1 (Lnc85) and FAL1, affect the invasion and migration of gastric, colorectal, HCC, respectively [49–52]. The primary tumor growth, cancer cells shedding and occupying the matrix, blood vessel

Table 1
Exosomal lncRNAs as tumor biomarkers in liquid biopsies.

Cancer type	Exosomal lncRNA	Liquid biopsy source	Effect	Ref
CRC	exoCRNDE-h	Serum	exoCRNDE-h high levels correlated with metastasis	[54]
	exoLNCV6_116109, 98390, 38772, 108266, 84003, and 98602	Plasma	Upregulated in early CRC stages, diagnostic potential	[55]
	ADAMTS9-AS1	Serum	Upregulated, diagnostic potential	[56]
	HOTTIP	Serum	Underexpressed, diagnostic and prognostic	[50]
RCC	Exo lnARSR	Plasma	Increased levels of Exo lnARSR related to sunitinib resistance, prognostic potential	[39]
	GAS5	Serum	Downregulated in NSCLC patients, diagnostic potential	[57]
	Exo HOTAIR	Serum	Upregulated exo HOTAIR is associated with neoadjuvant chemotherapy and tamoxifen hormone therapy response, predictive response	[58]
Glioblastoma	Exo HOTAIR	Serum	Overexpressed in glioblastoma patients, diagnostic potential	[59]
OSCC	Exo HOTAIR and MALAT-1	Saliva	Associated with OSCC lymph node metastasis	[60]
Bladder cancer	Exo MALAT1, SPRY4-IT1 and PCAT-1	Urine	Upregulated in bladder cancer patients, diagnostic potential	[61]
	Exo UCA1-201	Urine	Distinguishes between bladder cancer patients and non-malignant urinary disorders, diagnostic potential	[62]
GC	lncUEGC1	Plasma	Upregulated, diagnostic potential	[63]
	HOTTIP	Serum	Low expression, diagnosis and prognosis	[4, 50]
	CEBPA-AS1	Plasma	High levels, diagnostic	[64]
	lncRNA-GC1	Serum	Highly expressed, diagnostic and prognostic	[63]
	PCSK2-2:1	Serum	Upregulated, diagnostic	[65]
	H19	Serum	High expression, diagnostic	[66]
	PCGEM1	Serum	Upregulated, invasion and metastasis	[67]

Table 2
Exosomal lncRNAs implicated in therapy resistance.

Cancer type	LncRNA	Drug	Mechanism of action	Ref
Breast cancer [Human epidermal growth factor receptor 2 (HER2) positive]	SNHG14	Trastuzumab (TT)	Targets Bcl-2/Bax apoptosis pathway	[87]
Esophageal squamous cell carcinoma	PART1	Gefitinib (TT)	Upregulates Bcl-2 expression and acting as ceRNA against miR-129	[104]
Hepatocellular carcinoma;	Linc-VLDLR ABCG2	Sorafenib (TT), Camptothecin (CT), Doxorubicin (CT)	ATP-binding cassette sub-family G member 2	[84]
Hepatocellular carcinoma;	Linc-ROR	Sorafenib (TT), Doxorubicin (CT)	linc-ROR levels upregulated by TGF-β in extracellular vesicles.	[85]
Non-small cell lung cancer	RP11-838N2.4	Erlotinib (TT)	FOXO1 regulates this lncRNA negatively.	[105]
Glioblastoma multiforme	SBF2-AS1	Temozolomide (CT)	Competitively binds miR-151a-3p, resulting in DSB repairs	[80]
Renal cell carcinoma	lncARSR	Sunitinib (TT)	competitive binding to miR-34/miR-449, thus increasing AXL and c-MET expression	[91]

CT: Chemotherapy; TT: targeted therapy.

development, tumor cells leaking into the vascular system, thrombus formation, localized proliferation in secondary tissues and organs, and ultimately, metastatic cancer spreading further are all parts of the fundamental process of tumor metastasis, and exosomal lncRNAs play a crucial role in this phenomenon [53]. Table 1 illustrates the potential use of different exosomal lncRNAs in liquid biopsies.

3.2. Exosomal lncRNAs in tumor diagnosis and prognosis

Exosomal lncRNAs can reflect the characteristics of the primary tumor and thus monitor tumor progression by serving as stable and non-invasive biomarkers [19,54,68–70]. Various exosomal lncRNAs are reported to be significantly differentially expressed in cancer patients compared to healthy controls [71]. The unique selection of lncRNAs packaging into exosomes warrants further elucidation as these mechanisms remain poorly understood and are crucial in deciphering exosomal lncRNAs' mechanistic roles in tumor biology. For example, several exosomal lncRNAs (including the LNVC family) were revealed to be overexpressed in CRC patients' plasma [55]. On the other hand, the deregulated expression of HOTTIP exosomal lncRNA was shown to be significantly correlated with poor overall survival in CRC patients [72]. Contrarily, the increased expression of HOPPIT exosomal lncRNA was shown to be associated with TNM stages in gastric cancer (GC) patients, demonstrating the potential to serve as diagnostic and prognostic biomarkers. Furthermore, Li et al. showed the diagnostic potential of ADAMTS9-AS1 serum exosomal lncRNA, which was reported to be significantly under expressed in CRC patients than in healthy individuals [73]. Furthermore, exosomal lncRNA lncUEGC1 in stage I GC patients, demonstrated an increased diagnostic value compared to serum CEA [74]. Additionally, PCSK2-2:1 exosomal lncRNA was revealed to be considerably downregulated in GC patients, and this was linked to increased tumor size and tumor stage [75]. In addition, Guo et al. illustrated the correlation between exosomal lncRNA-GC1 and the tumor burden, with GC patients found to significantly accelerate from early to advanced GC stages [76]. Additionally, exosomal lncRNAs such as CEBPA-AS1 may serve as novel diagnostic biomarker in GC patients, as it was shown to have increased sensitivity and specificity, demonstrated by a higher ROC and AUC compared to those of traditional tumor markers [77]. Exosomal lncRNA H19 was also shown to have a better AUC than other commonly used GC markers [78]. Reports on the potential use of exosomal lncRNAs as diagnostic and prognostic non-invasive biomarkers in gastrointestinal cancers and other cancers are increasing.

Unlike classic lncRNAs, the exosome structure protects lncRNAs from rapid degradation, offering them an increased potential to be used as non-invasive cancer diagnostic and prognostic biomarkers. Some of these exosomal lncRNAs have been demonstrated to have greater sensitivity and specificity than the traditional cancer biomarkers. However, some of these exosomal lncRNAs are revealed to be expressed in a similar manner across different cancers, and this poses as a challenge in their clinical utility. Nonetheless, as the discoveries of these novel biomarkers advances, future studies should also be directed to underpinning the underlaying molecular mechanisms, with the aim to increase their clinical applications.

4. Exosomal lncRNAs in therapy resistance

The best therapies for primary localized tumors are radiation therapy and surgical excision. Nonetheless, pharmacological therapies are crucial to prevent recurrence or in the event of metastasis. At present, tumor drug treatment is primarily divided into four groups (chemotherapy, targeted therapy, immunotherapy and hormone therapy) based on each group's molecular target and mode of action. The notion that transferring exosomal lncRNA could alter target cells' characteristics and how they react to therapy is supported by numerous studies (Table 2). The part that exosomal lncRNAs play in encouraging therapy resistance will be discussed.

4.1. Chemotherapy

Chemotherapeutic medicines crudely restrict cell proliferation, impacting tumor and non-neoplastic cell growth, resulting in significant toxicity and side ramifications [79]. Temozolomide (TMZ) is an alkylating agent utilized in the treatment of glioblastoma multiforme (GBM). Several patients develop TMZ resistance, however, the molecular processes causing TMZ acquired desensitization remain unknown [80]. Zhang et al. revealed that exosomal lncRNA-SBF2 antisense RNA1 (lncRNA SBF2-AS1) encourages TMZ resistance. They studied the mechanism using GBM-TMZ tolerant and susceptible cell lines. They discovered that TMZ-resistant tissues and cell lines generated more SBF2-AS1 than susceptible ones using fluorescence in situ hybridization (FISH) and real-time reverse transcription PCR (qRT-PCR). The upregulation of the LncRNA SBF2-AS1 in TMZ-susceptible cell lines back-pedaled the chemotherapeutic impact of TMZ, offering TMZ resistance. On the contrary, knocking down lncSBF2- AS1 increased TMZ sensitivity. Exosome isolation and characterization showed substantial concentrations of SBF2-AS1, and TMZ-resistant patients had higher quantities of enriched-SBF2-AS1 exosomes in serum. Furthermore, SBF2-AS1 was found to sponge miR-151a-3p, increasing the levels of X-ray repair cross-complementing 4 (XRCC4) protein using Western blot, immunofluorescence, and RNA immunoprecipitation. XRCC4 is in charge of double-stranded DNA repair, which improves cell viability and makes cells resistant to TMZ-cytotoxicity [80]. M2 exosomal lncRNA SBF2-AS1 was also found to promote the progression of prostate cancer through upregulating the levels of X-linked inhibitor of apoptosis protein by binding to miR-122–5p [81]. Another M2-produced exosomal lncRNA, lncRNA H19 promotes autophagy in bladder cancer (BC) by stabilizing Unc-51-like autophagy activating kinase 1 (ULK1) [82].

Delivering altered lncRNA in M2-secreted exosomes can increase cancer development and chemoresistance [83].

Linc-VLDLR is a lncRNA that has a critical function in chemotherapy drug tolerance (camptothecin and doxorubicin) and sorafenib targeted therapy in HCC. HCC cell lines and derived-exosomes displayed elevated concentrations of linc-VLDLR after treatment with camptothecin, doxorubicin, and sorafenib. Incubation with linc-VLDLR-enriched EVs, on the other hand, suppressed apoptosis. The lncRNA was inhibited by interference RNA to investigate the molecular processes through which linc-VLDLR promotes therapy resistance: as a result, ATP-binding cassette, sub-family G member 2 (ABCG2), a drug ejecting protein, were under-expressed [84]. Another lncRNA, linc-ROR, was discovered to play a role in doxorubicin and sorafenib resistance in HCC. TFG (Transforming Growth Factor) and/or doxorubicin-sorafenib were used to treat several HCC cell lines. Consequently, exosomes possessed more significant linc-ROR quantities and were resistive to drug therapy. HCC cells were then co-cultured with linc-ROR-enriched exosomes, which resulted in improved viability after drug therapy. These findings support the involvement of exosomal linc-ROR in triggering drug tolerance in HCC. In addition, shutting down linc-ROR promoted death in HCC cells when exposed to doxorubicin and sorafenib. Furthermore, caspase 3/7 was shown to be elevated [85]. Ultimately, linc-VDLDR and linc-ROR have been shown to play an active role in exosome-moderated drug tolerance [86].

4.2. Targeted therapy

To avert the adverse effects of chemotherapy medications, targeted therapy evolved as the ideal solution. Advancements in molecular science have enabled the detection of cancer-related pathways. As a result, investigators developed particular medications to target these cancer-promoting molecules [79]. As previously stated, linc-VLDLR and linc-ROR have been demonstrated to induce tolerance to the targeted treatment sorafenib in HCC [86].

Dong et al. revealed that the lncRNA-small nucleolar RNA host gene 14 (SNHG14) is upregulated in trastuzumab-resistant HER2+ breast cancer cells compared to susceptible ones. Exosomes obtained from resistant cells produced the same results. Co-culture of SNHG14-enriched exosomes with susceptible HER2+ breast cancer cell lines resulted in a trastuzumab-desensitizing phenotype. The outcome was rectified by removing SNHG14. The processes through which the lncRNA SNHG14 causes trastuzumab tolerance are not fully understood, although a signal transduction reporter array revealed the relevance of the apoptotic regulator pathway Bcl-2/Bax [87].

Cetuximab is a monoclonal antibody used to treat colorectal cancer (CRC) that attaches to the EGFR (epidermal growth factor receptor) and causes it to degrade. Most tumors, however, are insensitive to cetuximab. As a result, predictive indicators for cetuximab resistance could aid in treatment choice. In this setting, UCA1 was found to be elevated in tolerant CRC cells in comparison to mother cells, suggesting that it could be a new biosignatures for cetuximab insensitivity [88].

Prostate Androgen-Regulated Transcript 1 (PART1) is a lncRNA that causes desensitization to gefitinib in esophageal squamous cell carcinoma. Gefitinib is a tyrosine kinase inhibitor that works by inhibiting several tyrosine kinases. PART1 is elevated in gefitinib-resistant cells. Extracellular PART1 was discovered to be contained in exosomes by FISH. In vivo nude mouse xenografts implanted with PART1-transfected TE1 cells revealed that when treated with gefitinib, PART1-TE1 tumors developed substantially quicker than controls. The molecular process of PART1-prompted gefitinib tolerance was also outlined: because PART1 competitively absorbs miR-129, Bcl-2 mRNA is no longer repressed, enhancing its protein expression and decreasing cell death. Exosomal PART1 could be employed as a therapy selecting biomarker in the clinical setting. Gefitinib resistance is indicated by elevated PART1 expression in serum exosomes [89].

Erlotinib, like gefitinib, is a tyrosin kinase blocker. Erlotinib tolerance is a common stumbling block in NSCLC treatment. Consequently, the significance of numerous exosomal lncRNAs in erlotinib tolerance has been investigated in order to identify potentially relevant molecules. The lncRNA RP11-838N2.4 has been found to be overexpressed in erlotinib-insensitive NSCLC cells. FOXO1 may regulate lncRNA expression by mobilizing histone deacetylases to its promoter region. Furthermore, exosomes from patients with erlotinib-tolerant NSCLC were substantially concentrated with RP11-838N2.4 [90].

The lncARSR [lncRNA-Activated in Renal Cell Carcinoma (RCC) with Sunitinib Resistance] was discovered in RCC by Qu et al. [91]. LncARSR upregulation is linked to an unsatisfactory reaction to the tyrosine kinase blocker sunitinib. Sunitinib desensitization is also caused by lncARSR exosomal transfer in the receiving cell. They also revealed how lncARSR enhances sunitinib resistance through molecular pathways. In a nutshell, the lncRNA connects to mir-34 and miR-449. This interactivity absorbs both miRNAs and enhances the levels of their downstream targets, c-MET and AXL, whose expression is responsible for sunitinib tolerance [91].

4.3. Hormone therapy

Hormone treatment is mainly focused on compounds that target hormone production or function in malignancies that are hormone dependent. A large percentage (75%) of breast tumors are hormone receptor positive [92,93]. Because both molecular subtypes respond to endocrine therapy, Tamoxifen, an ER blocker, is regarded as the first-line hormonal therapy for oestrogen receptor positive (ER+) breast neoplasia [94]. The lncRNA Urothelial cancer associated 1 (UCA1) was discovered by Xu et al. as an exosomal deliverer of tamoxifen treatment tolerance in breast neoplasia. Exosomes produced from tamoxifen-resistant breast cancer cells, LCC2, expressed more UCA1 than susceptible cells (MCF7). Tamoxifen-sensitive MCF7 cells were exposed to LCC2-derived exosomes (high UCA1 content), which reduced cell death after tamoxifen therapy. Exosomal UCA1 can be transported from tamoxifen-insensitive cells to sensitive cells, triggering cell death. Finally, tamoxifen-resistant cells may pass on exosomal UCA1 to sensitive cells, resulting in drug resistance [95]. The upregulation of LncRNA H16 is reported in 72.5% cases of breast cancer and is implicated in hormone therapy resistance in breast cancer [96]. Additionally the increased expression of lncRNA DSCAM-AS1 of potentially predicts a substantial possibility of hormone therapy resistance [97]. Other lncRNAs such as ERLC1 and LINP1 promote fulvestrant and tamoxifen in breast cancer, respectively [98,99].

4.4. Immunotherapy

The most studied immunotherapy is immune checkpoint blockage. Immune checkpoints are made up of several surface molecules that keep the immune system in balance and avoid autoimmune responses. Immune checkpoints allow tumor cells to avoid detection by the immune system. Tumor cells undergo multiple modifications that diminish their antigenicity by increasing immunoinhibitory chemicals and recruiting immunosuppressive cells to the local tumortumor microenvironment [100]. The first immune checkpoint inhibitors licensed by the FDA target programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1). These immunotherapeutic medicines inhibit PD-1 or PD-L1, boosting the immune reaction to the tumor. For example, the FDA licensed PD-1 antibodies nivolumab and pembrolizumab in 2014 and 2017, respectively, for advanced metastatic melanoma, CRC, NSCLC, RCC, castration-insensitive prostate cancer, and other solid insensitive tumors, including TNBC [101]. TNBC accounts for 20% of all breast cancers. Because the absence of hormone receptor expression precludes the use of hormonal and targeted therapy, chemotherapy is the sole means of treatment. The emergence of immunotherapeutic medicines like pembrolizumab has provided fresh options for therapy for TNBC. Several TNBC patients, nonetheless, are insensitive to PD-1 blocking

drugs [102]. The lncRNA LINK-A was found to be elevated in these patients. Furthermore, it has been discovered that LINK-1 mediates the breakdown of the antigen peptide-loading complex (PLC). As a result, LINK-1 reduces antigenicity and increases PD-1 immune checkpoint inhibitor insensitivity [103]. It remains to be determined whether LINK-A may be transmitted via exosomes to convey PD-1 inhibitor resistance. As a result, investigation should be directed in this particular direction as well [86].

Tumor-associated macrophages are vital in encouraging cancer development and modulating tumor immune avoidance. TAMs associated lncRNAs are implicated in cancer cell proliferation, angiogenesis and therapy tolerance. Liu et al. revealed the association of the lncRNA LINC02096 with immunotherapy outcomes. Previously described mechanisms of immunotherapy resistance include tumor antigen expression loss, antigen presentation issues, constitutive PD-L1 expression, and T-cell malfunction [83–85]. TAM associated LINC02096 was shown to mediate immunotherapy resistance through increasing the expression of the immunological checkpoint markers PD-L1/IDO-1, leading to T-cell inactivation and impaired responsiveness to *anti*-PD-1 mAb treatment in esophageal squamous cell carcinoma [86].

Recent research suggests that lncRNAs can directly influence mRNA expression, potentially contributing to treatment resistance [87,88]. The elevated expression of cyclin B1 (CCB1) in NSCLC is linked to the cis modulation of lnc-CENPH-1 and lnc-CENPH-2 and the trans modulation of lnc-ZFP3-3. The association between CCB1 and lnc-ZFP3-3-TAF1 combination was identified as a critical component in immunotherapy tolerance [89].

5. Exosomal communication in tumor microenvironment: shaping interactions

Cells communicate via cell-to-cell junctions and through soluble factors [106]. Exosomes released by malignant cells consist of a variety of inflammatory and immunosuppressive molecules, including macrophage migration inhibitory factor (MIF) [107] and PD-L1 [108], which cause vascular leakiness [109], inflammatory infiltration [110], extracellular matrix (ECM) remodeling [111], and immunological inhibition in neighbouring or distal normal tissues or organs [112]. As functional role-players, exosomal lncRNAs have a pivotal function in the genetic and epigenetic modulation of intercellular signaling. As a result, increasing interest and effort are being put into understanding the precise role and mechanisms of exosomal lncRNAs in neoplasia [113].

In the TME, cancer cells interact with stromal cells, macrophages, extracellular matrix elements, endothelial cells, immune cells, and myeloid-derived suppressor cells (MDSCs) through secreting exosomal lncRNAs [114]. This interaction aids in creating a microenvironment that supports tumor development, progression, and metastasis in tumor cells [115]. Exosomal lncRNAs significantly affect angiogenesis, immune suppression, drug resistance, growth, and metastasis in TME [116]. Exosomes enhance and regulate lncRNA activity by delivering them to the distal area, where they are absorbed by cells via endocytosis [115,116]. As primary cell-to-cell communicators, exosomes and their cargo are involved in establishing and transferring therapy resistance [117]. For example, lncARSR can share sunitinib resistance in renal cell carcinoma through interacting with hnRNPA2B1, resulting in the packaging of lncARSR into exosomes to drug-susceptible cells. In addition, lncARSR ceRNA interferes with the AKT, ERK, and STAT3 pathways by sponging miR-34 and miR-449, which impedes the effect of sunitinib [39]. Exosomal lncRNA H19 in breast neoplasia was shown to activate adriamycin tolerance [118]. Limited reports on exosomal lncRNAs on cancer drug resistance further illustrate the research gap in deciphering the mechanisms of exosomal lncRNAs. This will open doors to innovative combinatorial chemotherapeutic treatments with drugs targeting exosomal lncRNAs linked to therapy resistance [119]. Furthermore, exosomal lncRNAs regulate TME by controlling energy metabolism, thus promoting tumor progression. Hypoxic circumstances cause cancer cells to rewire their energy metabolism and develop cancerous phenotypes. Elevated amounts of exosomal linc-ROR released by hypoxic HCC support glycolysis and counter hypoxia. Linc-ROR upregulates the expression of miRNA-145, HIF-1α, and pyruvate dehydrogenase kinase isoenzyme 1 (PDK1), thus encouraging cell proliferation and viability [120].

Exosomal lncRNA role on the macrophages has also been reported. In the TME, macrophages are also known as the tumor-associated macrophages (TAMs). TAMs are a pivotal population of innate immune cells [121]. Depending on their activation status, TAMs may exert pro-or--*anti*-tumor properties in the TME. Following stimulation, the TAMs can be changed to M1 or M2 macrophages. The classical M1 macrophages are most disposed to possess anti-tumor immunity properties and produce pro-inflammatory cytokines. On the contrary, the M2 macrophages induce anti-inflammation and favor tumor progression [122]. TAMs' conversion to M1 or M2 is important in tumor progression and treatment [123]. Thus, the interactivity between TAMs and tumor cells in the TME through the exosomes warrants deeper understanding. In glioblastoma, exosomal lncRNA TALC can be conveyed to microglia, activating the ENO1/p38 MAPK axis and promoting M2 polarisation [124]. Another investigation by Xing et al. showed that lncRNA XIST is downregulated, and this promotes exosomal miRNA-503 production, enhanced PD-L1 expression, M2 polarisation and tumor-promoting activities in brain and breast cancers [125].

In nasopharyngeal carcinoma (NPC), exosomal lncRNA TP73-AS1 can be transported by macrophages, leading to M2 polarisation, upregulated migration of macrophages, and tube formation [126]. In breast cancer, exosomal lncRNA BCRT1 targets the miR-1303/PTBP3 axis, thereby promoting M2 polarisation, angiogenesis, and tumor cell migration. In osteosarcoma, exosomal lncRNA ELFN1-AS1 enhances the polarisation of M2 macrophages and osteosarcoma progression [127]. Additionally, pancreatic exosomal lncRNA FGD5-AS1 induces M2 polarisation and promotes pancreatic cancer cells' proliferation and invasion [128]. In renal cell carcinoma, exosomal lncRNA ARSR activates the STA3 pathway, promoting M2 polarisation and tumor progression [129]. Furthermore, exosomal lncRNA AP000439.2 activates STAT3/NF–B signaling, enhancing M2 polarisation in clear cell renal carcinoma [130]. While there is still a lack of adequate data in this field, emerging reports illustrate the preferential influence of exosomal lncRNAs on M2 polarisation in the TME and cancer progression.

6. Exosomal lncRNAs and immunomodulation: orchestrating immune responses

6.1. Immune cells

In the TME, immune cells secrete cytokines, chemokines, proteolytic enzymes, and growth factors. These secreted molecules promote tumor progression, modulate immune evasion, or kill tumor cells [131]. Exosomes play an essential role in the signaling processes where the immune cells are incorporated into the TME [132]. Tumor cells' exosomes can directly trigger the natural killer (NK) cells, B cells, T cells, and macrophages [25]. Additionally, the stimulation of carcinogenic cues can produce immune-inducing exosomes, resulting in tumor clearance [133]. It is also reported that exosomes can be immune suppressive, inhibiting the function of NK cells and effector CD4 and CD8 cells [25]. Furthermore, exosomes can impede differentiation of DCs and MDSCs [134]. On the other hand, exosomal RNAs can also stimulate myeloid cell communities [135]. Nevertheless, the function of RNA -signaling pathways in the suppression or activation of adaptive and innate immunity is still understudied, further broadening the research gap on mechanistic evidence of the exosomal lncRNAs in cancer progression. NK cells are a significant population of immune cells, and they kill tumor cells or produce cytokines that strengthen the immune response [136]. Exosomal lncRNAs can be transmitted into NK cells, promoting or inhibiting tumor progression in the TME. Upregulated lncRNA GAS5

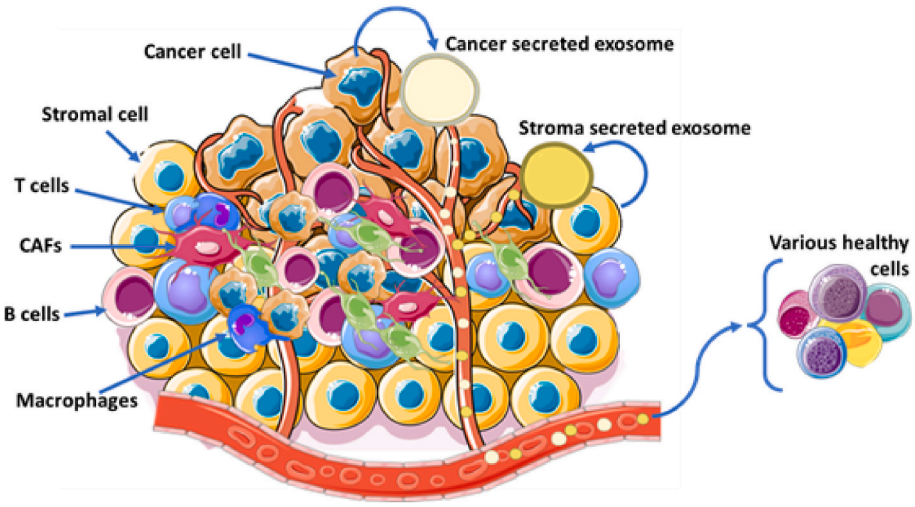

Fig. 3. Exosomes are released by various types of cells including stromal cells, CAFs, various types of immune cells etc in TME. Exosomes modulates TME by engaging in cell-to-cell communication within the TME through their various contents. Circulating exosomal contents are released into the receptor cells which carry same genetic/epigenetic information of primary tumor site, regulating inter-and-intracellular signaling.

enhances NK cells' cytotoxicity in various cancer cells [137,138]. In CRC, NK cell-mediated cytotoxicity is inhibited by the exosomal lncRNA SNHG10 promoting effects on transforming growth factor beta (TGF-β) signaling pathway [109].

Antiviral signaling and responses may be vital in understanding these mechanisms as exosomal RNAs play a significant part in the propagation of these impulses. Exosome release and delivery to healthy spectator cells may culminate in exosome-transferred viral RNA by pattern recognition receptors (PRRs). Forinstance, Hepatitis C (HCV) virus-infected cells can pass the HCV genomic RNA by exosomes to the healthy cells. The exosome-encoded HCV RNA is then recognized by the recipient cells as a pathogen-associated molecular pattern (PAMP). Thus, the anti-viral signaling will then be activated despite the absence of the actual virus [139]. During the Epstein-Barr virus (EBV) infection, the exosomal EBV RNA informs adjacent cells of an infection. The anti-viral reaction in the adjacent cells is triggered by the EBV latent-infected cells. This is facilitated by the transmission of EBV 5'ppp RNA bereft of the protecting RNA binding proteins [140]. While exosomal RNAsmay be crucial in antiviral reactions, it is not yet established whether the RNA recognition pathways in the TME activate or suppress the anti-tumor immune responses. Understanding the immune inducing or inhibiting exosomal RNA roles in the TME can aid in identifying exosome biomarkers and help in designing combinatorial therapies that can benefit patients [3]. Fig. 3 shows the exosomes' involvement in the TME.

6.2. *Exosomal lncRNAs role in immunomodulation*

The host immune responses are primarily divided into two, the innate and adaptive immunity against antigens. A crosstalk communication occurs between tumor cells and the TME [141]. The TME functions as a fundamental immune regulator in tumor development and progression by offering either stimulatory or inhibitory signals [141]. The TME is an active proponent of cancer progression, as opposed to being a silent spectator, supporting cancer survival, invasion and metastasis [142]. Immune surveillance is evaded by the exchange of stimulatory impulses between the immune cells and tumor cells in the TME [143,144]. Emerging reports demonstrate the key role of exosomes in immune modulation regulation, thus contributing to an immunosuppressive TME [145]. For instance, immunotherapy resistance in melanoma patients is mediated by the CD73 expression of exosomes in the serum, inhibiting T cells' immune response [146]. In pancreaticneoplasia, secreted exosomes can enhance the transformation of tumor-related macrophages to M2 macrophages, thus favouring tumor metastasis [147]. In colorectal cancer, produced exosomes inducted the regulatory T cells' (Tregs) expansion, constructing an immunosuppressive TME and promoting cancer progression [148]. Thus, exosomes can regulate innate and adaptive immune cells in the TME, modulating tumor development and therapy.

Exosomal lncRNAs are active participants during the interplay and exchange of physiological signals between the tumor and the non-tumor cells in the TME. Forinstance, stromal cells including endothelial cells and CAFs, communicate with tumor cells via exosomal lncRNAs. CAFs can secrete inflammatory factors in the TME or inhibit the immune cells' functioning, thus promoting immune suppression [149]. In addition, inflammatory cytokines including IL-6 can participate in tumor activity modulation [150]. In eosophageal squamous cell carcinoma (ESCC), the lncRNA POU3F3 can enhance the change of normal fibroblasts (NFs) into CAFs. Additionally, exosomal lncRNAs moderated immune modulation in the TME can be attributed to the invasion of immune cells into the TME. These immune cells which include tumor-related macrophages (TAMs), NK cells, neutrophils, the T and B cells, interact with the tumor cells in the TME to either promote or inhibit tumor effects [117,151,152].

Exosomal lncRNAs have also been revealed to modulate the PD1/PD-L1 interaction to escape the immune cells' attack in different cancers. This was demonstrated on ESCC inducing high PD-1 expression on Bregs, activating TLR4/MAPK signaling pathways and enhancing B cell-mediated immunosuppression [153]. In CRC, exosomal lncRNA KCNQ1OT1 effects inhibit PD-L1 ubiquitination, thus inhibiting the evasion of immunological surveillance by $CD8^{+}$ T cells [154]. On the other hand, in HCC, exosomal lncRNA PCED1B-AS1 enhances PD-L1 and PD-L2 expression, suppressing T cells and macrophages and promoting tumor progression [155]. Thus, exosomal lncRNAs can either exert tumor promoting or tumor inhibiting properties in the TME, as well as promoting tumor's immune surveillance escape by enhancing M2 and Bregs immunosuppression and by increasing PD-L1 and PD-L2 expression on tumor cells. Blocking the activity of exosomal lncRNA-mediated ligand/receptor (PD-1/PD-L1) interaction by immune checkpoint inhibitors may be key in enhancing anti-tumor immunity [156]. However, these may require extensive immunoregulatory mechanistic studies, as these are multifaceted molecules involved in both physiology and pathophysiology.

7. Precision medicine and beyond: Personalized approaches to RNA-based therapeutics

Advances in RNA-based therapeutics exists, however, standard methods on the extraction of pure and efficient exosomal lncNRAs are still lacking. This may be an ideal starting point to the translational application of exosomal lncRNAs. Nonetheless, exosomal lncRNAs are surfacing as unique stable biosignatures in tumor diagnosis, prognosis, therapeutic targets and important candidates in deciphering TME and immunomodulation mechanisms. Furthermore, the exosome membrane structures providing protective barriers to the cargo, need to be overcome. While selected lncRNAs may exists inside exosomes and also as traditional lncRNAs, this section discusses the RNA-based therapeutics, which may provide insights of the potential clinical utility of exosomal lncRNAs. Many lncRNAs exhibit abnormal expression in malignancies and can be found in the bodily fluids of cancer patients [157,158]. Dysregulated lncRNA expression is thought to be a predictor of how aggressive a malignancy is [159]. LncRNAs are therefore desirable therapeutic targets for the management of cancer [160]. There are numerous treatment methods that target lncRNAs, including antisense oligonucleotides (ASOs), RNA interference (RNAi) technology, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 genome editing, small molecule inhibitors [161].

7.1. Antisense oligonucleotides (ASOs)

Single-stranded synthetic oligonucleotides known as ASOs target a variety of RNAs, including lncRNAs, which can interfere with the synthesis of mature RNA, protein complexes, or RNA splicing [162]. ASOs are currently being investigated as therapeutic and druggable strands to target pathways relevant to malignancies [163]. ASOs complementary to a ncRNA sequence are utilized as antagonists to adversely influence gene expression since ncRNAs, including lncRNAs, play a significant part in controlling gene expression in malignancies [164]. Additionally, ASOs have a better knockdown efficiency for nuclear lncRNAs than siRNAs [165]. Bester and colleagues used specific locked nucleic acid (LNA)-enhanced ASOs to suppress GAS6-AS2 lnRNA which resulted in increased K562 cell susceptibility to cytarabine therapy [166]. Notably, the MMTV-PyMT mouse mammary carcinoma model's cancer progression was suppressed by the use of two distinct gapmeRs (LNA-conjugated chimeric single-strand ASOs) targeting separate regions of the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [167,168]. According to a different study, the new LNA-gapmeR ASO that targets MALAT1 inhibits the expression of proteasome subunit genes and triggers apoptotic pathways in multiple myeloma (MM) cells [163]. In another study, breast cancer cells become more resistant to tamoxifen when the lncRNA UCA1 is suppressed by siRNAs or shRNA [162]. The optimization of siRNAs and LNA ASOs for lncRNA targeting is crucial despite significant efforts being made to develop promising and functional ASOs since heat instabilities and ribonuclease sensitivity have to be confirmed. Peptide nucleic acids (PNA) are being evaluated as a cutting-edge cancer treatment strategy. The first encouraging result showed that using PNAs to target HOX transcript antisense RNA (HOTAIR) in breast cancer decreased matrix metalloprotease 9 (MMP-9) and Interleukin 6, which boosted susceptibility to platinum-based treatment [169].

Future developments in ASO therapy concentrate on developing more effective delivery methods in addition to the best target sequences with the highest specificity [170]. Although different ASO transport mechanisms are being explored, oligonucleotide delivery still plays a crucial role in therapeutic procedures. Lipid-based delivery methods are most frequently used [171]. Exosomes are currently being studied as prospective carriers for novel medicinal distribution strategies. Exosomes can include therapeutic oligonucleotides that target modulatory RNAs like miRNAs and lncRNAs as a single or combined treatment approach to control the growth of cancer [172]. Exosomes that are employed for treatment distribution are commonly derived from the cell or can be created using a variety of engineering procedures. Exosomes carrying the cell-specific payloads can be used as a starting point. In order to produce exosomes with the desired cargo, cells can directly get injected with exogenous substances including proteins, lipids, and nucleic acids (mRNAs, miRNAs, lncRNAs, etc.). Second, using various transfection techniques including electroporation, sonication, lipofection, or calcium chloride, nucleic acids can be directly loaded into exosomes. Exosomes that have been changed can be given in bulk to recieving cells to change the expression of certain genes [173,174]. Electroporation or other methods are ineffective for delivering nucleic acids directly into exosomes since the process necessitates repeated purification and there is a significant risk of widespread exosome aggregation during loading [175,176]. The effectiveness of productive exosome-nucleic acid transport may therefore be increased by actively packing nucleic acids into exosomes by protein or peptide binding to a particular RNA sequence [175]. Through the development of an active packaging device and a cytosolic transfer aid, a new delivery technique for the packaging of particular RNAs into exosomes has been created. Exosomes with particular packaged mRNAs can be produced by these Exosomal transfer into cells (EXOtic devices), which can then be gathered and delivered to the target cells. Exosome concentration is unnecessary with these EXOtic devices [177]. Since some exosomes might interrelate with the immune system and impact the target destination because of the differences of in antigen presentation on the exosomes, it is imperative to choose the most suited natural or engineered exosomes [178]. Exosomes from red blood cells were used in a recent study to electroporate *anti*-miR-125 b ASOs into exosomes that were subsequently transfected into MOLM13 cells to release the p53 network's silenced genes [179]. This strategy's effect could be applied for breast cancer cells [180], and even different lncRNAs can be taken into consideration for the targeted therapy by exosome-ASO administration, as miR-125 b is a documented oncomiR in drug resistant breast cancers [181].

7.2. Engineering of exosomes with lncRNA cargo as a therapy strategy

The therapeutic use of manufactured nanoscale carriers has been hampered by their short half-life in physiological fluids, poor efficiency in bridging biological barriers such as the blood-brain barrier (BBB), and possible immunogenicity and toxicity [182,183]. Exosomes, naturally generated from cells, are gaining interest as a solution to overcome drawbacks [184,185]. The bulk of unaltered injected exosomes end up in the liver or spleen rather than where tumor cells are located [186,187]. As a result, an engineering technique should be implemented to alter exosomes in order to increase their anti-tumor effectiveness [187]. LncRNAs are upregulated in many tumors [188–192]. Exosome-linked lncRNAs have been shown to participate in tissue repair and regeneration [193]. LncRNAs that preferentially accumulate in exosomes regulate tumor formation, metastasis, angiogenesis, and drug resistance, influencing the progression of malignancies [193]. A significant number of exosomes act as an organic carrier for lncRNAs; hence, lncRNAs utilized in the bioengineering of exosomes must be appropriately identified [160]. LncRNAs exhibit both tumor-inhibitory and tumor-promoting characteristics. Exosomes must be modified to transport tumor-suppressing lncRNAs. However, in addition to the tumor suppressive effect, exosomal lncRNAs may improve the susceptibility of cancerous cells to medicines [160].

Several engineered lncRNA that demonstrate therapeutic potential may be transported to target areas via exosomes include LOC285194, which decreased tumor development in NSCLC by modulating p53 [194]. FOXF1 Adjacent Noncoding Developmental Regulatory RNA (FENDRR) also decreased the progression of NSCLC [195]. The engineering of the tumor-targeting exosome via altering exosomes with the c (RGDyk) peptide and loading lncRNA MEG3 proved to be a viable therapeutic strategy for osteosarcoma [196]. Similarly lncRNA MEG3

delivered to NSCLC cells enhanced the sensitivity to paclitaxel, resulting in lower proliferation and higher p53 expression [197]. Furthermore the delivery of lncRNAs steroid receptor RNA activator 1 and lncRNA LINC00520 inhibited tumor growth and migration in osteosarcoma cells and cutaneous squamous cell carcinoma respectively [198,199]. Therefore, naturally existing lncRNAs packaged in exosomes might be employed as tumor therapy molecules with a site-specific effect [200].

7.3. RNA interference (RNAi) technology

Exosomal lncRNA treatments, such as siRNA, are one of the promising therapeutic approaches since exosomes transporting lncRNAs participate in immune modulation in cancer. siRNA, which has double-stranded RNAs consisting of 20–24 nucleotides, has the ability to reduce mRNA translation, inhibit mRNA transcription, and promote mRNA or pre-mRNA degradation to control gene expression [201]. Additionally, siRNAs can be supplied to target cells and integrated into their genomes, resulting in the post-transcriptional control of lncRNAs. Target lncRNAs are spliced and degraded by some siRNAs when they complementarily join with target lncRNAs to form an RNA-induced silencing complex [202]. Accordingly, siRNAs can prevent abnormal lncRNA expression, which will consequently slow tumor growth [203]. According to Chen et al. [204] suppressing M2 polarisation in NSCLC cells with siRNAs can prevent the formation of tumors. Exosomes are employed as delivery moderators to shield siRNAs from endosome-moderated destruction due to their high biocompatibility. In the case of TNBC, elevated lncRNA DARS-AS1 was discovered to promote tumor development and metastasis, whereas DARS-AS1 siRNA-loaded exosomes prevented TNBC growth and metastasis [205]. Guo and colleagues discovered that the application of M2-*Exo*-siRNA H19 suppressed BC development whereas elevated lncRNA H19 in M2-produced exosomes encouraged BC cell proliferation [82]. These findings suggest that exosomal siRNAs that target exosomal lncRNAs could be beneficial in cancer therapy [83].

7.4. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 genome editing

CRISPR/Cas9 can be utilized for silencing or knocking out loci that express lncRNA [33]. Following the CRISPR/CAS system's entry into the cell, gRNAs direct the CAS enzyme to identify certain DNA sequences on PAM that are complementary to the gRNA. The CAS enzyme then cuts the DNA double strand, altering or by triggering an alteration via a frameshift, which ultimately silences the altered gene [206]. The main challenges with CRISPR/Cas9 gene therapy are off-target consequences. Target delivery optimization is the key to successful treatment. Exosomes and nanomaterials can prevent medication aggregation or degradation when used as therapeutic carriers, and they are linked to effective targeting. As a result, effective therapeutic genome editing depends on the secure and effective intracellular delivery of CRISPR/-Cas9 [207]. He and colleagues demonstrated that the utilization of microvesicles (MVS) produced from epithelial cells as a carrier to transfer CRISPR/Cas9 constituents to tumor cells revealed potent anti-tumor effects against xenograft tumors, and this may potentially be a safe CRISPR/Cas9 delivery platform for cancer patients [208].

7.5. Small molecule inhibitors

Small molecule inhibitors primarily attach to lncRNAs' higher structural sections, which resemble protein targets [209]. High-throughput sequencing may be utilized in screening and identifying small molecule drugs that may inhibit RNA. ASO is a member of a group of medications that attach to the lncRNA transcriptome by base pairing [210]. Based on this mechanism, the drug gapmeR targets RNA targets with extra covalent bonds to 2′-O and 4′-C nucleotide rings in order to attract the RNA-H enzyme and cause target breakdown [211].

7.6. Combination of targeted lncRNA therapeutics with immunotherapy

The most efficient approach to treating cancer may involve integrating targeted lncRNA therapeutics with immunotherapy antibodies or chemotherapy agents to optimize the effectiveness of antitumor therapies [212]. Immunotherapy has completely changed how cancer is treated, particularly when it comes to therapies that target different parts of the immune-oncology cycle, such as immune checkpoint blockade (ICB) and chimeric antigen receptor T cell therapy (CAR-T). The MHCs on cancer cells that express T cell-recognized neoantigens are a major factor in ICB therapeutic effectiveness. It has been discovered that tumor-related lncRNAs inhibit antigen presentation to help tumor cells elude the immune system [212]. For instance, lncRNA LINK-A may affect the stability of MHC-1 in cancer cells. Therapy with LINK-A LNAs in addition to ICB can effectively slow tumor growth and lengthen the survival of tumor-bearing mice, demonstrating their mutually beneficial efficiency [103]. The justification for this t approach is that LINK-A LNAs' reduction of LINK-A expression reestablishes the antigen presentation pathway of tumorcells, increasing the malignancy's susceptibility to ICB therapy. It should be noted that LNA therapy has no effect on how immune cells like macrophages, MDSCs, and CTLs are distributed [103]. Therefore, it is possible that combination therapy using lncRNA ASOs or LNAs and ICBs will have an additive effect on human antitumor immunity [212].

Treatment of hematological malignancies has benefited significantly from adoptive T cell (ATC) therapies, particularly CAR-T therapy [213,214]. However, there are still certain limitations to the effectiveness of CAR-T treatment in solid malignant tumors. Recent research has demonstrated that lncRNAs served as the supplemental targets of CAR-T therapy. LncRNA-NKILA significantly increases T cells' susceptibility to activation-induced cell death (AICD) through reducing NF–B activity, which helps tumor cells evade the immune system. In the patient-derived xenograft (PDX) model, NKILA shRNA-transfected $CD8^+$ T cells were implanted into immunocompromised mice, significantly inhibiting tumor development and defeating tumor immune evasion by enhancing infiltration and cytotoxicity of CLTs and lowering the AICDs [215]. These results show that manipulating lncRNAs can enhance the effectiveness of ATC treatment for tumors [212]. Similar to this, Mineo and colleagues discovered that lncRNA-INCR1 suppression boosted CAR-T cell effectiveness *in vivo* by regulating tumor IFN-γ signaling and increased sensitivity of cancerous cells to T cell-moderated death [216]. When combined with CAR-T cell therapy, engineering lncRNAs could be a potential immunotherapeutic approach [212].

The optimal combination immunotherapy, however, would improve effector cell function while diminishing that of the protector cell [217]. Accordingly, increasing anticancerous lncRNAs and lowering tumorigenic lncRNAs while using numerous lncRNAs simultaneously for integrated therapy may be an alternative efficacious method. In addition to lowering the dosage and each drug's adverse effects, multiple-method combination therapy, and combined modulation of various immune cells (i.e., Suppressing the infiltration and impact of MDSCs while enhancing the infiltration and cytotoxicity of CTLs) also increase the overall efficacy of immunotherapy [212].

8. Common pitfalls impeding exosomal lncRNA research

Exosomal lncRNAs have a promising potential use in cancer care and management. However, there are also some limitations. These include the lack of a sizeable quantity of exosomal lncRNAs' discovery. The mechanism of action of the already discovered exosomal lncRNAs also remains largely to be elucidated. Furthermore, there is an absence of reliable conventional extraction techniques for exosomal lncRNAs. The available extraction methods cannot simultaneously ensure exosomal content, purity and biological activity. Even though documented in animal studies and independent reports of medical data, the sensitivity and specificity of exosomal lncRNAs as biomarkers still requires

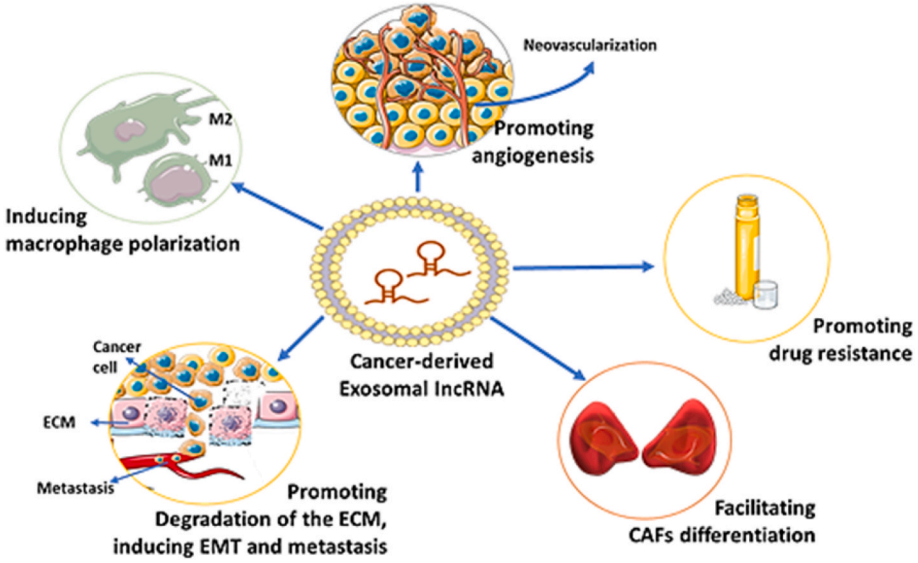

Fig. 4. Role of exosomal lncRNA in cancer. Cancer associated exosomal lncRNAs are associated with cancer progression by encouraging the degradation of the extracellular matrix (ECM) and induction of epithelial mesenchymal transition (EMT) associated with metastasis and drug resistance. Furthermore, exosomal lnRNA are associated with macrophages polarisation within the TME of which the protumorous M2 phenotype is favoured. Facilitating the differentiation of cancer associated fibroblast (CAFs) further adds to tumor progression and therapy resistance.

improvement. Furthermore, exosomal lncRNAs are multi-edged swords, acting on a broad range of targets. Thus, various exosomal lncRNAs can act on different targets, or one lncRNA can be targeted by different regulatory molecules, or different exosomal lncRNAs may act on an identical target. Furthermore, one particular exosomal lncRNA can serve as a double-edged sword, a tumor suppressor in a particular kind of tumor and an oncogene in others. This poses as a challenge in constructing a comprehensive network of exosomal lncRNAs regulatory mechanisms.

9. Conclusions and future directions: expanding frontiers in understanding and exploiting exosomal lncRNA functions

Exosomal lncRNAs' role in tumor progression is understudied. This is exacerbated by their role as competing endogenous RNAs, either targeting or being targeting by a broad range of targets. Exosomes are produced in higher amounts, ~10 times more by tumor cells compared to normal cells. This results in increased exosome concentrations in cancer patients' blood. These organelles (exosomes), perform a vital function in tumor progression, aberrant metabolism and immune dysfunction, as they carry unique genetic information of the original cells, transferring it to recipient cells. The TME is a required cellular environment for tumor progression and metastasis. Exosomal lncRNAs are emerging as key mediators between tumor cells and the TME, regulating the intercellular crosstalk. These exosomal lncRNAs regulate tumor progression by modulating key signaling pathways, EMT, energy metabolism, angiogenesis and remodeling the surrounding microenvironment into a TME. Exosomal lncRNAs are released by stromal cells and can be transferred to tumor cells, regulating tumor growth. Most of the emerging studies are independent pre-clinical and clinical studies and these necessitate the additional and validation of multiple studies of exosomal lncRNAs in the translational and clinical settings. Furthermore, standard methods on the extraction of pure and efficient exosomal lncNRAs are still lacking and this may be a good starting point to the translational application of exosomal lncRNAs. Nonetheless, exosomal lncRNAs are surfacing as unique stable biosignatures in malignancy diagnosis, prognosis and important candidates in deciphering TME and immunomodulation mechanisms. Fig. 4 summarises the roles of exosomal lncRNA in tumor biology and immunomodulation. Although it is an expanding field, exosomal lncRNA research is novel. Their exploratory roles in tumor diagnosis and prognosis is key in the identification of the cells of origin, and may therefore be useful in cell biopsies. Although their clinical application needs further development, exosomal lncRNA mechanistic understanding remains fundamental in this paradigm shift.

CRediT authorship contribution statement

Rahaba Marima: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Afra Basera:** Writing – original draft. **Thabiso Miya:** Writing – original draft. **Botle Precious Damane:** Writing – review & editing. **Jeyalakshmi Kandhavelu:** Writing – review & editing. **Sheefa Mirza:** Writing – review & editing. **Clement Penny:** Writing – review & editing. **Zodwa Dlamini:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

All the authors declare no conflict of interest.

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