Exosomes as carriers transporting long non-coding RNAs: Molecular characteristics and their function in cancer (Review)

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Abstract. Long non-coding RNAs (lncRNAs) comprise a sizeable class of non-coding RNAs with a length of over 200 base pairs. Little is known about their biological function, although over 20,000 lncRNAs have been annotated in the human genome. Through a diverse range of mechanisms, their primary function is in the regulation of the transcription of protein-coding genes. lncRNA transcriptional activation can result from a group of nucleus-retained and chromatin-associated lncRNAs, which function as scaffolds in the cis/trans recruitment of transcription factors, co-activators or chromatin remodelers, and/or promoter enhancers. Exosomes are released as extracellular vesicles and they are produced by endocytic pathways. Their synthesis is initiated by various processes including ceramide synthesis, release of intracellular Ca2+ or acid-base balance disorders. Prior to vesicle creation, selective cargo loading occurs in the Endosomal Sorting Complex Required for Transport. Participation of endosomal sorting proteins such as tetraspanins or specific sumoylated proteins required for transport has been indicated in research. The endosomal-sorting complex consists of four components, these induce the formation of multivesicular bodies and the induction of membrane deformation to form exosomes. Nanovesicles could be formed inside multivesicular bodies to allow transport outside the cell or digestion in lysosomes. The molecular content of exosomes is more heterogeneous than its synthesis process, with different cargoes being examined inside vesicles with regard to the type or stage of cancers. This paper will review the importance of lncRNAs as crucial molecular content of exosomes, indicating its involvement in tumour suppression, pro-tumorigenic events and the development of novel therapeutic approaches in the near future. Further studies of their mechanisms of function are essential, as well as overcoming several challenges to gain a clearer insight to the approaches for the best clinical application.

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1. Introduction

The term transcriptome encompasses the complete set of RNA molecules applying to an entire organism or specific cell type, making it more dynamic than the genome. It comprises several types of transcripts which are responsible for changes in gene expression. Two major classes of regulatory non-coding RNAs (ncRNAs) which lack any transcriptive capability include microRNAs and long non-coding RNAs (lncRNAs). They play a significant role in diverse cellular processes from enabling normal development to disease progression, as well as cell communication. A valuable example of a biological carrier that can transport abundant quantities of lncRNA is that of the exosome: A type of extracellular vesicle involved in cell-to-cell communication and disease transmission. Its role has been documented in both physiological conditions and pathological changes such as cancer development, where they are responsible for the regulation of various processes including immunosuppression, proliferation and induction of pre-metastatic niche formation. In this review, the role of a number of exosomal lncRNA molecules will be discussed.

2. Characteristics of exosomes

The first scientific report to examine the possibility that intracellular structures could be associated with the process of budding vesicles bearing receptors during maturation, using ferritin-labelled proteins and anti-IgG, recorded the
externalization of transferrin receptors into the intercellular space during sheep reticulocyte maturation (1). The term exosome was later proposed in 1987 (2).

Exosomes are small spherical nanovesicles ranging from 20 to 120 nm (3,4). They belong to the group of membrane-derived vesicles known as extracellular vesicles (EVs), together with oncosomes, ectosomes or apoptotic bodies (5). The classification of each vesicle to its specific group depends on genesis, composition, size and density (see Table I). Extracellular vesicles can be secreted constitutively or as a result of specific induction (6). The origin of exosomes is linked to the creation of multivesicular bodies (MVBs) in the endosomal pathway: MVBs are structures with a lipid bilayer and a density of 1.12-1.19 g/Ml (7) and which display 5' nucleotidase activity (8).

Exosomes are released from many types of healthy or tumour cells, although more abundantly in the latter (9), and can be found in the tumour microenvironment (TME) and blood samples of cancer patients (10). Physiologically, exosomes can be found in urine (10), sperm (3), amniotic fluid (9) and various other biological fluids. The role of exosomes in metastasis, angiogenesis and epithelial-to-mesenchymal transition (EMT) has been confirmed in cancer development by various studies (9). Exosomes released by tumour cells were shown to constitute a leading source of antigens for dendritic cells inducing antitumour immune responses (11). The physiological functions of exosomes include cellular communication, immunity, infections, elimination of waste products and signalling (12). There is also evidence of their participation in aging-related diseases i.e. neurodegeneration when different signal molecules and various processes including ceramide synthesis and Ca²⁺ signalling (3). Proteins that interact with the cell membrane and perform lipid bilayer deformation are epsin, amphiphysin, endofilin, syndapin and dynamin (4).

Biogenesis. Exosome secretions and their molecular mechanisms are rather obscure, since their release is regulated by several signal molecules and various processes including ceramide synthesis and Ca²⁺ signalling (3). Proteins that interact with the cell membrane and perform lipid bilayer deformation are epsin, amphiphysin, endofilin, syndapin and dynamin (4). The biogenesis follows the following sequence: The process begins with membrane invagination and exosome release to cytoplasm, followed by early endosome (EE) formation, and then the formation of intraluminal vesicles (ILVs) inside the late endosome (LE).

Under both normal and pathological conditions, exosomes have an endocytic origin and are released by different types of cells. Although exosomes typically mimic the composition of the parent cells, they may contain a few signature proteins. Following the formation of exosomes within the endocytic pathway, they are released from the plasma membrane via MVBs from early endosome maturation and may further fuse with lysosomes or the plasma membrane. The most common and well-known mechanism of cargo sorting is based on the action of proteins from Endosomal Sorting Complex Required for Transport (ESCRT) (6). When this pathway is inactivated, there is a possibility to recruit sumoylated protein hnRNPA2B1 [it binds microRNA (14)] or maintain the signal through tetraspanin-enriched microdomains (TEMs) composed of transmembrane glycoproteins (8,15). The schematic of ESCRT complex based on yeast, is shown in Fig. 1.

Molecular content. Nanovesicle formation exhibits some characteristic stages of biogenesis and involves specific structures present in the cell. The selective mechanism of transporting cargo to the exosome interior is a more heterogenous process, as evidenced by their varied content, even in different types and stages of cancer development (8). The composition of exosomes contains countless types of proteins, including cytokines and growth factors, lipids or nucleic acids (3), including characteristic biomarkers such as CD63, CD81, CD9, TSG-101, ALIX or HSP70 which allow direct identification of exosomes (6).

Proteins. The profile of the proteins within the vesicles consists of cytoplasmic proteins, cell membrane proteins or...
proteins from endosomes; however, no proteins from organelles have been detected (6). These proteins include a number of exosomal molecules, such as those connected with MVB biogenesis (e.g., ALIX, TSG-101) (6), ESCRT components (3), transport and fusion proteins (annexin, Rab-GTP, flotillin) and heat shock cognate (HSc). Other important ones include integrins, tetraspanins or subunits of G proteins. The tumour exosomes (TEXs) include additional molecules that participate in the EMT process including matrix metalloproteinases (MMPs), IL-6, TGF-β and immunosupression factors (Fas l, Trail and Gal-9 that stimulates T cell apoptosis) (8). Some of them are presented in Table III.

**Lipids.** The lipid composition of exosomes is distinct from that of the cell membrane: it is rich in components such as cholesterol, sphingomyelin, glycerophospholipids, phosphatidylinositol, ceramide or phosphatidylserine, as well as prostaglandins and leukotrienes (6). The lipid content in exosomes is higher than that of the parent cell except phosphatidylcholine which is ordinarily decreased (24). An example of exosomal lipid activity is the differentiation of bone-marrow myeloid cells into myeloid-derived suppressor cells (MDSCs) by prostaglandin E2. The accumulation of MDSCs leads to immunosupression, which provides favourable conditions for metastasis (8). The participation of lipids in the biogenesis of exosomes is summarized below (Table IV).

**Nucleic acids.** Exosomes also can include different types of RNA or DNA such as mRNA, miRNA, lncRNA, dsDNA, RNA-ROR (regulator of reprogramming) (3), and therefore play a vital role in regulating signaling pathways and gene expression (refer to Table V). These DNA and RNA molecules may be transferred into recipient cell by the fusion of exosome and cell membranes, aiding the regulation of large numbers of signaling pathways or expression of genes (3). Many studies indicate elevated levels of lncRNA in extracellular exosomes compared to parent cells (25,26). This can be attributed to the action of nucleotide patterns that are present in transcripts

| Extracellular vesicles | Size       | Density            | Origin of vesicles |
|------------------------|------------|--------------------|--------------------|
| Exosomes               | 20-120 nm  | 1.12-1.19 g/ml     | Multivesicular body|
| Ectosomes              | ~0.1-1 µm  | ~1.16 g/ml         | Cell membrane      |
| Apoptotic bodies       | 0.05-5 µm  | 1.24-1.28 g/ml     | Cell membrane      |
| Oncosomes              | 1-10 µm    | Not specified      | Cell membrane      |

![Figure 1. ESCRT formation and cargo sorting of multivesicular body (based on (85)).](image-url)
Table II. Selected proteins involved in fusion of MVB with cell membrane and in exosome secretion [based on (3,4,7,87)].

| Protein | Proteins family | Function |
|---------|-----------------|----------|
| Rab7; Rab11 | RabGTP | Promotes proper protein attachment in pathways dependent on calcium ions |
| Rab27 (a, b) | RabGTP | Regulates the stages of exosome secretion, controls the location of MVB |
| Rab35 | RabGTP | Regulates exosomes secretion by interacting with GTP-activating protein-TBC1(Tre-2/Bub2/Cdc16) |
| RAL-1 | RasGTP | Recruiting the Syx-5 protein, thereby mediating in fusion of membranes |
| Syx-5 (Syntaxin5) | SNARE | Stimulates fusion of MVB with cell membrane |
| VAMP7 (Vesicle-Associated Membrane Protein) | SNARE | Necessary for MVB fusion with cell membrane |
| YKT6 | SNARE | Mediates the release of exosomes from the cell |

Figure 2. Biogenesis and destination of exosomes inside and outside the cell [based on (4,5,7,8,86)]. Nanovesicles in the multivesicular body can be transferred to lysosomes or be released from the cell to enter into blood vessels or fuse with neighboring cells. When entering the target cells, the exosome cargo can exert a different biological effect, resulting in changes in cell physiology for example-reprogramming it into a cancer cell.
as cis-acting elements responsible for targeting them into exosomes (27).

The purpose of this review is to highlight the significance of lncRNA as a pivotal molecule inside exosomes. Therefore, it will summarize the role of various exosomal lncRNAs, together with their function in carcinogenesis and in other biological processes.

3. lncRNA

The functional annotation of 60,770 full length longer cDNAs and rare transcripts in the mouse transcriptome resulted in the discovery of a novel class of non-coding cDNAs, among which ~80% of the transcripts are not spliced (28). The lncRNAs constitute a class of transcripts that does not encode proteins and whose length exceeds 200 bp (29). This group includes several heterogenous molecules that are difficult to categorize: LncRNAs can be divided into long intergenic non-coding RNAs (lincRNAs), long intronic non-coding RNAs and half-STau1-binding site RNAs (½sbsRNAs) (30). Depending on the DNA coding strand, the lncRNAs can be classified as sense or antisense transcripts (31);

Table III. Examples of exosomal molecules involved in tumour progression, immunosuppression and apoptosis [based on (3,4,6,10,88,89)].

| Type of molecule in exosome | Function | Type of cells |
|-----------------------------|----------|--------------|
| ITG αβ4; ITG αβ1           | Connected with metastasis to the lungs, promotes TEXs adhesion in the lungs | Lung cancer cells |
| ITG αβ5                     | Connected with metastasis to the liver, binding to Kupffer cells | Liver cancer cells |
| TGF-β; IL-10; MCP-1 (Monocyte Chemoattractant Protein-I) | Promote cell migration | Lung cancer cells, melanoma cells |
| MHC-II (Major Histocompatibility Complex-II) | Stimulation of CD4+ cells | B lymphocytes, DC cells |
| OVA (Ovalbumin)             | Inhibition of immune response | Melanoma cells |
| EGFR (Epidermal Growth Factor Receptor); KRAS ( Kirsten RA Sarcoma viral oncogene homolog) | Proliferation, resistance to treatment | Lung cancer cells |
| EGFRvIII (EGFR variant III) | Anti-apoptotic abilities | Glioma cells |
| MDR-1 (Multi-Drug Resistance) | Resistance for drug | Prostate cancer cells |
| HER2 (Human Epidermal growth factor Receptor 2) | Resistance to treatment with Trastuzumab | Breast cancer cells |

Table IV. The examples of lipids involved in formation and secretion of exosomes [based on (9)].

| Lipid | Function |
|-------|----------|
| Phosphatidylserine | Participation in microautophagy connected with HSC70 protein (process of exosomes synthesis) |
| LysoBisPhosphatidic (LBPA) | Change in membrane dynamics (in collaboration with ALIX) |
| BisMonocyclicglycerolPhosphate (BMP) | Binding to ALIX protein; (BMP formed by PhosphoLipase D2) |
| Ceramide | Involved in the biosynthesis of exosomes and packaging miRNA into them (in a process independent of the ESCRT machinery) |
| Cholesterol | Participation in secretion of FLOT2-positive exosomes |
| Lipid rafts (cholesterol-rich sphingolipid microdomains) | Participation in the biogenesis of exosomes inside MSCs (Mesenchymal Stem Cells) |
| Phosphatidylcholine transporter ABCA3 | Participation in the biogenesis of exosomes derived from B-cell lymphoma |
that IncRNAs act like a ‘sponge’-leading to miRNA recruitment into EVs, or possibly to provide the mechanisms required for microRNA loading (13).

These findings confirm both the diversity of IncRNAs and their participation in carcinogenesis by demonstrating their influence on the promotion of angiogenesis, protein stability or miRNA inhibition by acting as a sponge. In addition, as IncRNAs are detected in TExs or apoptotic bodies, and have high stability during circulation, they could be considered as potential cancer biomarkers (33); however, some studies indicate they may display tumour suppression behavior through the blocking of the transcription of apoptosis-inhibiting genes and stimulation of p53 expression (34) or the structural modification of chromatin (35).

**IncRNAs as protumorigenic molecules.** Numerous studies implicate IncRNAs as cancer-associated molecules that are enriched in exosomes. A classic feature of the tumour microenvironment is hypoxia, which has a notable impact on cancer progression. Activation of its pathway via the transcription factor hypoxia inducible factor (HIF) plays a part in metastasis and a more aggressive phenotype. The role of IncRNAs in hypoxia-driven cancer progression came into view recently, where these hypoxia-responsive IncRNAs play a critical part in regulating hypoxic gene expressions (36). The next subsections will present the characteristics of the most frequent types.

**HOTAIR:** HOX Transcript Antisense RNA has been associated with progression and poor prognosis in patients with squamous cell carcinoma (SCC), hepatocellular carcinoma (HCC), urothelial bladder cancer (UBC) or colorectal cancer (CRC) (37). Yan et al (38) report the involvement of HOTAIR in the repression of WIF-1-a protein implicated in the Wnt signaling pathway. Moreover, epigenetic regulation is also achievable: it participates in the migration, invasion or proliferation, potentiating through silencing of miR-205 in bladder cancer. In addition, UBC cells displayed increased invasion with migration corresponding to regulation of the EMT pathway, which was confirmed by knockdown of HOTAIR. This resulted in reduced invasiveness by influencing genes connected with EMT such as MMP1 (Matrix metalloproteinase-1), ZEB1 (Zinc finger E-box-binding homeobox 1), TWIST1 (Twist-related protein 1), SNAI1 (Snail family zinc finger 1), ZO-1 (Zonula occludens 1), LAMC2 (Lamin, gamma 3), LAMB3 (Laminin, beta 3) or ABL2 (ABL proto-oncogene 2) (37). Studies by Xie et al, have shown that salivary HOTAIR could be used as biomarker in diagnostics: it had good discriminatory power for differentiating pancreatic cancer from healthy patients and benign pancreatic tumour (39, 40). In addition to its contribution in cancerous diseases, HOTAIR has also been described to play a role in rheumatoid arthritis, where its transcript activates MMP-2 and MMP-13 in synoviocytes and osteoclasts. This could promote joint and cartilage matrix cessation advancing joint destruction. Furthermore, HOTAIR-loaded exosomes with enriched IncRNA activate macrophages and influence immune response (41).

**MALAT-1:** Metastasis-Associated Lung Adenocarcinoma Transcript 1 or Nuclear-Enriched Abundant Transcript 2 (NEAT-2) was the first IncRNA to be associated with metastasis in Non-Small Cell Lung Cancer (NSCLC). This transcript, similar to the HOTAIR IncRNA, is also connected with migration or tumour growth induction. Zhang et al (42), indicated increased expression of transcript compared to healthy controls, and an association with higher TNM stage in patients with cancer. In vitro study knockdown of MALAT-1 in cancer cell lines significantly inhibited cell proliferation and colony formation, although it also induced cell cycle arrest and cell apoptosis due to a decrease in S phase progression. In addition, cyclin D1 and cyclin D2 downregulation was also observed, suggesting that MALAT-1 was involved in acceleration of the cell cycle. This indicates that MALAT-1 can be an important therapeutic target when developing treatments for NSCLC patients, because of its participation in the malignant phenotype of cancer through gene expression regulation (43).

Alongside NSCLC, MALAT-1 has been proposed as a mediator of angiogenesis in Thyroid Cancer. Huang et al (44), found it to play a role in the secretion of the fibroblast growth factor 2 (FGF) protein from tumour-associated macrophages (TAMs), which led to vascularization, promotion of proliferation, invasion and migration of cancer cells. Nonetheless, MALAT-1 participation in releasing inflammatory cytokines or FGF2 secretion was predominantly blocked by overexpression of FGF2.

**ZFAS1:** Initial studies concerning the Zinc Finger AntiSense 1 (ZFAS1) IncRNA refer to alveolar development in the mammary gland, with a proposed role in the regulation of alveolar development and epithelial cell differentiation in the mammary gland (45). The transcript has been found to promote cancer progression by cell cycle regulation through cyclin-dependent kinase 1 (CDK1) interaction or destabilization of the p53 protein. The level of ZFAS1 was also upregulated in exosomes from HCC, CRC and gastric cancer (GC). Pan et al (46), noticed that overexpression of this transcript leads to proliferation and migration of GC cells and ZFAS1-positive exosomes which can be internalized by MKN-28 cells. Knockdown of ZFAS1 inhibited the migration, proliferation and EMT process; however, it also induced cell cycle arrest and programmed cell death, serving as a potential tumour suppressor. These findings have been attributed to decreased ERK, Bcl-2 and increased Bax protein levels. Additionally, ZFAS1 knockdown was observed to suppress cell migration by decreasing the expression of EMT transcription factors such as Slug or Twist. These findings suggest that ZFAS1 could promote metastasis by cell cycle acceleration or support EMT playing a pivotal role in GC diagnosis (47).

**H19:** H19 IncRNA is also involved in tumor metastasis and has been described as a master factor in cancer biology due to its frequent deregulation in almost all tumours, both in the initiation and progression steps (48). H19 is connected with the downregulation of E-Cadherin, which influences cell adhesion and leads to spread of cancer cells. In addition, Conigliaro et al (49) investigated H19 as a pro-angiogenic molecule promoting cell-to-cell adhesion (CD90+ cells with endothelial cell monolayer) and association with increased expression of VEGF and ICAM1 transcripts which in turn leads to new vessel development. H19 may also act as an epigenetic modulator or as miRNA sponge (50). In conclusion, this type of IncRNA could have a range of impacts on target cells and some of its functions still remain unknown;
Table V. The examples of nucleic acids that occur in exosomes [based on (3,6,90)].

| Nucleic acid | Length in base pairs (bp) | Function |
|-------------|--------------------------|----------|
| mRNA        | ~3,250 bp (for TMPRSS2 in prostate cancer, *TransMembrane PRotease Serine 2*) | Participation in metastasis, progression of cancer |
| IncRNA      | More than 200 bp         | Regulation of gene expression at transcriptional, posttranscriptional and epigenetic levels |
| dsDNA       | More than 2,500 bp       | Participation in neoplasm (more frequent occurrences in tumour exosomes than exosomes from normal cells) |
| RNA-ROR     | ~2,600 bp                | Resistance to chemotherapy in HepatoCellular Carcinoma, promoting cancerogenesis through specific histone methylation |

nevertheless, H19 has been proposed as a potential therapeutic target (e.g., in HCC) (51).

*POU3F3*: *In vitro* studies indicate that this transcript increases viability and cell proliferation in gliomas and its overexpression is associated with tumour grading (52). Hu et al (53) investigated whether exosomal POU3F3 from glioma cells could promote angiogenesis and its effect on endothelial cells. They indicate that IncRNA enriched the exosomes regulating the migration, proliferation and angiogenesis of Human Brain Microvascular Endothelial Cells (HBMECs) in both *in vitro* and *in vivo* studies. Silencing POU3F3 using shRNA decreased the migratory ability of endothelial cells but did not affect their motility. POU3F3 overexpression in HBMECs caused by IncRNA enriched exosome internalization, and significantly upregulated the transcript level of bFGF, bFGFR, Angio and VEGFA. These findings indicate that POU3F3 IncRNA can be an essential molecule in cell-to-cell communication or a regulator of angiogenesis in glioma cells (53).

*TUC339*: One of IncRNA transcribed from ultraconserved elements (UCEs) is TUC339. UCEs are 100% maintained genomic sequences that are greater than 200 bases in length and are conserved across human, mouse and rat genomes (54). The localization of these elements is connected with fragile sites and cancer-associated regions of the genome. Overexpression of this type of IncRNA has been reported in HCC (55). A study on the role of exosomal ultraconserved IncRNA in modulating target cell phenotype as a result of genomic changes found that TUC339 upregulation in HCC cell lines resulted in an enhancement of cell growth and a reduction of adhesion to cell-extracellular matrix (ECM). The knockdown of TUC339 decreased proliferation and altered the expression of a total of 843 genes, 469 of which were inhibited (56).

*ROR*: LncRNA ROR participates in liver cancer through disruption in TGF-β pathway. Although TGF-β has been related to cancer chemoresistance, the molecular actions involved in this event remain unknown. Takahashi et al (57), identified a possibly mechanism by which IncRNA may mediate chemoresistance dependent on TGF-β. They indicate that TGF-β reduced the sensitivity of HCC cells to sorafenib or doxorubicin, with a further reduction of sorafenib-dependent caspase 3/7 activity, leading to inhibition of the apoptosis process. Moreover, the release of extracellular vesicles and packaging of IncRNA within vesicles were also modulated by TGF-β. One of the selectively enriched exosomal IncRNAs thought to be a potential mediator of chemoresistance is RNA-ROR. Using a molecular pathway connected with p53 dependent signaling, IncRNA can contribute to tumor development by inhibiting apoptosis through the repression of p53. Additionally, knockdown of this IncRNA results in increased expression of Caspase 8 and GADD45B, leading to apoptosis induction and growth arrest. These data suggest that IncRNA ROR can be an important mediator in cell-to-cell communication and its contribution in chemoresistance has been confirmed in research. Inhibition of this transcript resulted in reversion of drug resistance, leading to cell death (58).

*VLDLR*: One of the long-intergenic non-coding RNA transcripts that support HCC development is called VLDLR (59). By showing that knockdown of this RNA can result in cell cycle arrest in G1/S phase, Takahashi et al (60), confirmed that it regulates HCC cell proliferation. Moreover, the quantity of IncRNA was increased in both HCC cells and extracellular vesicles following chemotherapeutic stress caused by sorafenib, doxorubicin and camptothecin, thus enhancing cell viability. Furthermore, the extracellular transfer of VLDLR to adjacent tumour cells could participate in chemoresistance through the modulation of ABCG2 gene expression.

The summary of the other lncRNA molecules that participate in tumour development is presented in Table VI.

*Suppressor function of IncRNA*. In contrast to the IncRNAs with pro-cancerous properties, there is also another group of transcripts that could support normal cells rather than stimulating their conversion into a neoplastic phenotype (61).

*GAS5*: Several studies have implied that the Growth Arrest Specific 5 gene molecule has not been connected with cancer progression, as its expression has been observed to be reduced in various cancer types (62,63). Pickard et al (64), noticed that GAS5 participates in apoptosis regulation in prostate cancer cells. They indicated that the high expression of GAS5 level reduces tumour cell survival and hence induces pro-apoptotic activity. On the other hand, when
**Table VI. Functions of chosen IncRNA molecules in numerous tumour types [based on (91-102)].**

| IncRNA     | Function                                                                                                                                | Tumor type                                | (Refs.) |
|------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------|
| ARSR       | Resistance to sunitinib; overexpression leads to poor response of renal cancer patients; promoting c-MET expression                         | Renal cell carcinoma (RCC)                | (91)    |
| MEG3       | Cell cycle arrest; decreases apoptosis by regulation of miR-21                                                                         | Cervical cancer (CC)                      | (92, 93)|
| RMRP       | Acts as a miR-206 sponge and modulate the cell cycle by regulating the Cyclin D2 expression                                             | Gastric cancer (GC)                       | (94)    |
| NEAT1      | Promotes cancer progression through regulating CDK6 mediated by influence on miR-107                                                  | Laryngeal squamous                        | (95)    |
| UCA1       | Enhances cell proliferation, migration, invasion, EMT process                                                                          | Bladder cancer (BC)                       | (96)    |
| HULC       | Induces angiogenesis and modulates VEGF expression; upregulates sphingosine kinase 1 (SPHK1) by miR-107/E2F1 pathway                     | Liver cancer (LC)                         | (97, 98)|
| TUG1       | Promotes radioresistance and EMT transition; enhance proliferation and migration                                                        | Bladder cancer (BC)                       | (99, 100)|
| HOTTIP     | Increases the chemoresistance by Wnt/β-catenin pathway activation                                                                         | Osteosarcoma                              | (101)   |
| CCAT2      | Upregulates VEGF and TGFβ, promotes angiogenesis, decreases apoptosis by elevated Bcl-2 expression and inhibition of Bax and caspase-3 | Glioma cancer                             | (102)   |

**Table VII. Participation of IncRNAs in various diseases [based on (77, 103-110)].**

| IncRNA     | Disease                                         | Function                                                                                                                                  | (Refs.) |
|------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------|
| CRNDE-h    | Colorectal cancer (CRC)                         | Promotes metabolic changes through insulin/IGF signaling                                                                               | (103)   |
| p21        | Prostate cancer (PCa)                          | Alter gene expression by modulating mRNA translation and suppressing the p53 or Wnt/β-catenin pathway                                               | (104)   |
| PCA3       | Prostate cancer (PCa)                          | Modulates the survival of cells downstream of androgen receptor signaling                                                                | (105)   |
| BCAR4      | Breast cancer (BC)                             | Convert phenotype into an estrogen-independent, antiestrogen-resistant; tamoxifen resistance via HER2 signaling                             | (106)   |
| ATB        | Hepatocellular carcinoma (HCC)                 | Suppresses E-cadherin, leading to progression of epithelial tumor cells via inducing EMT                                                  | (107)   |
| ANRIL      | Non-small cell lung carcinoma (NSCLC)          | Affects proliferation and apoptosis using suppression of KLF2 and P21 transcription                                                          | (108)   |
| LINC00152  | Gastric cancer (GCA)                           | Connects with depth of invasion among gastric cancer patients                                                                             | (109)   |
| RP11-445H22.4 | Breast cancer (BC)                        | Its expression levels correlated with estrogen receptor (ER), progesterone receptor (PR), and menopausal status of the breast cancer patients; this molecule showed a remarkable improvement compared with CEA | (110)   |
| RP11-1382.1 | Chronic kidney disease (CKD)                   | Unknown function                                                                                                                         | (77)    |
GAS5 was downregulated, programmed cell death was diminished but growth arrest was not. In prostate carcinoma GAS5 has been found to bind to the receptor domain and inhibit transcriptional stimulation, leading to increased death of tumour cells (65).

**PARTICL:** Some studies also confirmed the role of lncRNAs in the methylation process in response to radiation. One of this lncRNA is PARTICL (promoter of MAT2A antisense radiation-induced circulating long non-coding RNA) a trans-acting mediator of DNA, and histone lysine methyla-

tion, a clever component for gene silencing (66). The findings indicate that in low dose irradiation, PARTICL can enhance EZH2 (enhancer of zeste homolog 2) expression, which in turn catalyzes the addition of methyl groups to histone H3 at lysine 27. Moreover, there was also an observed increase in the activity of the DNMT1 enzyme (DNA methyltransferase 1), global methyleme enhancement methyleme regulation e.g., CpG island methylation of WWOX gene. Finally, speculation about PARTICL as an epigenetic modifying platform targeting chromatin structure modulation through recruitment of PRC2 (Polycomb Repressive Complex 2) has been proposed; this has been proposed to act by the binding of lncRNA to a subunit of PRC2 called SUZ12 (Suppressor of Zeste 12). These data indicate that PARTICL interlinks regulators of epigenetic modifications that may affect the suppression of transcription (67).

**CCND1:** Another lncRNA found in exosomes (68) and connected with ionizing radiation-dependent transcription (69) is ncrNA CCND1 (cyclin D1). This single strand transcript binds to the TLS (translocated in liposarcoma) modulator, thus recruiting it to CCND1 promoter and inducing negative regulation of gene transcription. In addition, it also blocks the activity of CREB (cAMP response element binding) and p300 proteins.

**EXO1-4:** The four molecules that occur abundantly in exosomes (68) and connected with ionizing radiation-dependent transcription (69) is ncrNA CCND1 (cyclin D1). This single strand transcript binds to the TLS (translocated in liposarcoma) modulator, thus recruiting it to CCND1 promoter and inducing negative regulation of gene transcription. In addition, it also blocks the activity of CREB (cAMP response element binding) and p300 proteins.

**EXO1-4:** The four molecules that occur abundantly in exosomes as a result of maintaining full stability of lncRNA in extracellular vesicles as mentioned earlier, these transcripts can be taken up by target cells with their full functionality preserved (78). This make EVs effective nanocarriers that are capable of regulating lncRNAs expression in cancer cells (79). An attractive potential tumour therapy that requires further development maintaining high levels of tumour suppressor lncRNAs or destabilizing oncogenic ones (80). H19 is an example of the use of pro-tumorigenic long non-coding transcripts in the specific targeting of tumour cells. The regulatory sequence of this lncRNA was used in the successful formation of the BC-819 plasmid. In vivo this construct encodes the toxin Diphtheria Toxin A (DTA) which provided encouraging results in the treatment of bladder or colon cancer, as well as pancreas carcinoma or NSclc (81).

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**EXO1-4:** The four molecules that occur abundantly in exosomes as a result of maintaining full stability of lncRNA in extracellular vesicles as mentioned earlier, these transcripts can be taken up by target cells with their full functionality preserved (78). This make EVs effective nanocarriers that are capable of regulating lncRNAs expression in cancer cells (79). An attractive potential tumour therapy that requires further development maintaining high levels of tumour suppressor lncRNAs or destabilizing oncogenic ones (80). H19 is an example of the use of pro-tumorigenic long non-coding transcripts in the specific targeting of tumour cells. The regulatory sequence of this lncRNA was used in the successful formation of the BC-819 plasmid. In vivo this construct encodes the toxin Diphtheria Toxin A (DTA) which provided encouraging results in the treatment of bladder or colon cancer, as well as pancreas carcinoma or NSclc (81).

There are still several challenges that needs to be tackled in order to provide efficient EV-based lncRNAs therapeutics for clinical application, but the current state of research offers promise.

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Authors’ contributions

DK drafted the manuscript, designed the figures, and researched the literature. DK and EP designed the article. EP, AKB and RH revised the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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