



# Exosomal miRNAs and lncRNAs: The Modulator Keys of Cancer-Associated Fibroblasts in the Genesis and Progression of Malignant Neoplasms

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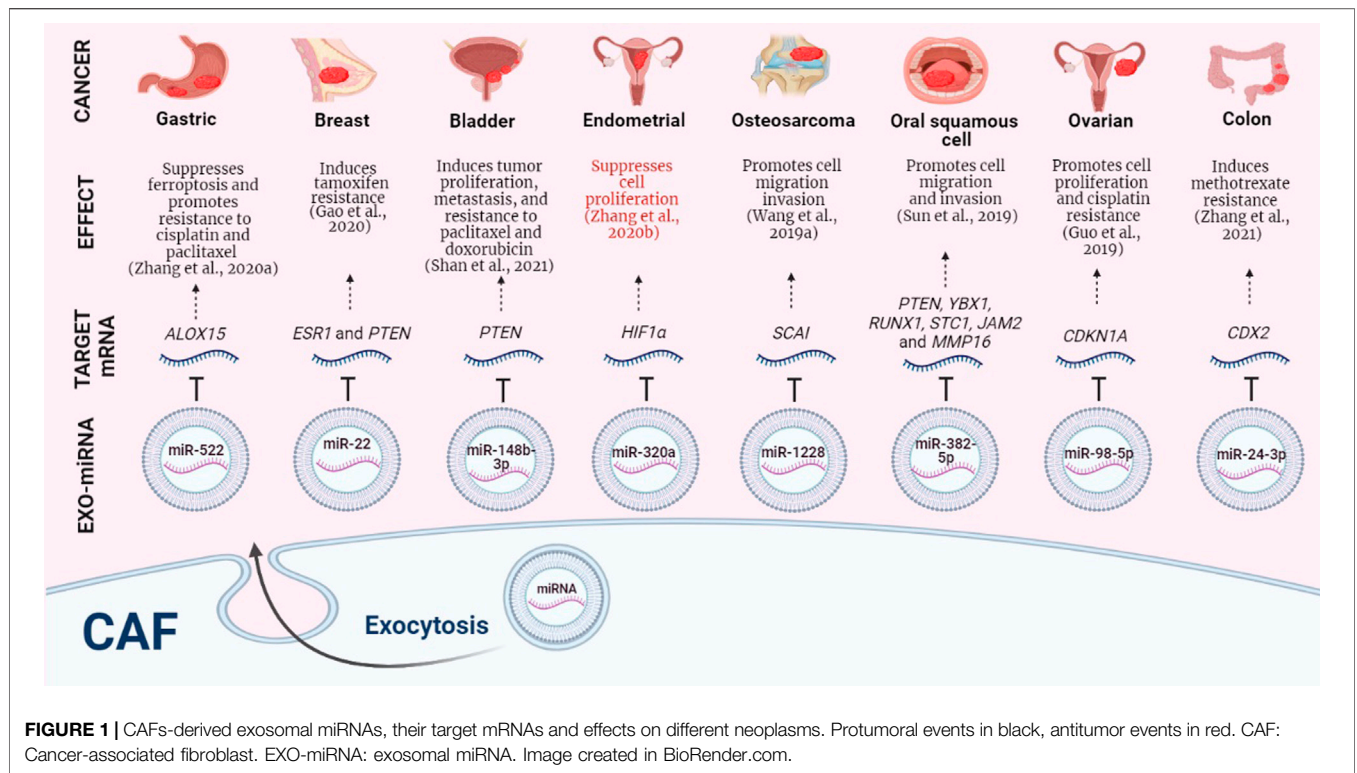
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The tumor microenvironment is made up of a universe of molecular and cellular components that promote or inhibit the development of neoplasms. Among the molecular elements are cytokines, metalloproteinases, proteins, mitochondrial DNA, and nucleic acids, within which the ncRNAs: miRNAs and lncRNAs stand out due to their direct modulating effects on the genesis and progression of various cancers. Regarding cellular elements, the solid tumor microenvironment is made up of tumor cells, healthy adjacent epithelial cells, immune system cells, endothelial cells, and stromal cells, such as cancer-associated fibroblasts, which are capable of generating a modulating communication network with the other components of the tumor microenvironment through, among other mechanisms, the secretion of exosomal vesicles loaded with miRNAs and lncRNAs. These ncRNAs are key pieces in developing neoplasms since they have diverse effects on cancer cells and healthy cells, favoring or negatively regulating protumoral cellular events, such as migration, invasion, proliferation, metastasis, epithelial-mesenchymal transition, and resistance to treatment. Due to the growing number of relevant evidence in recent years, this work focused on reviewing, analyzing, highlighting, and showing the current state of research on exosomal ncRNAs derived from cancer-associated fibroblasts and their effects on different neoplasms. A future perspective on using these ncRNAs as real therapeutic tools in the treatment of cancer patients is also proposed.

**Keywords:** cancer, cancer-associated fibroblast, tumor microenvironment, exosomes, miRNAs, lncRNAs

## INTRODUCTION

Malignant tumors consist of cancer cells and tumor-associated host cells (De Wever et al., 2014), the interaction between tumor microenvironment (TME) and tumor cells plays a key role in cancer progression (Dayan et al., 2012; Ali et al., 2015; Shah et al., 2015; Vered et al., 2015; Ringuette Goulet et al., 2018; Zhang Y.-F. et al., 2019; Dou et al., 2020; Wu et al., 2020). Remarkably, the dynamic interplay between cancer-associated fibroblasts (CAFs), cancer cells, and healthy cells has an essential role during tumor initiation and growth (Zhao et al., 2016; Li K. et al., 2020; Lv et al., 2020). In recent years, exosomes have gained relevance due to their regulatory role in the carcinogenesis of different neoplasms (Nilsson



et al., 2009; Ramteke et al., 2015; Donnarumma et al., 2017; Seo et al., 2018; Zhang Y. et al., 2019; Lee et al., 2020). Exosomes are MHC class I- and class II-bearing nanovesicles of endocytic origin; their size is in the range of 30–100 nm (Admyre et al., 2007; Nilsson et al., 2009). Exosomes can participate in intercellular communication between cells that make up the TME by transmitting intracellular cargoes (Achreja et al., 2017; Qin et al., 2019), their content can be miscellaneous and include macromolecules such as cytokines (Mashouri et al., 2019), metalloproteinases (Shimoda et al., 2014), proteins (Mathivanan et al., 2010; Zhang Y.-F. et al., 2019; Zhao et al., 2020), mitochondrial DNA (mtDNA) (Sansone et al., 2017) and can be enriched with different types of RNAs, such as messenger RNAs (mRNAs) (Gener Lahav et al., 2019), microRNAs [miRNAs or miR-, single-stranded non-coding RNAs (ncRNAs) of 20 nucleotides in length that are endogenously expressed (Beer mann et al., 2016)] (Théry, 2011; Nouraei et al., 2016; Qin et al., 2019), about this type of ncRNAs, Dragomir et al., in their work entitled “*SnapShot: Unconventional miRNA Functions*,” mention that miRNAs can regulate gene expression at the post-transcriptional level in a conventional way by binding to mRNAs, resulting in the disintegration of target mRNAs and inhibition of translation, additionally, the authors also highlight in an exceptional way that through various mechanisms, such as the activation of Toll-like receptors, the upregulation of protein expression, the targeting of mitochondrial transcripts, the direct activation of transcription, among others, miRNAs can carry out their regulatory functions in an unconventional way (Dragomir et al., 2018), and long non-coding RNAs (lncRNAs, transcripts that are longer than 200 nucleotides and do not harbor protein-coding signatures (Beer mann et al., 2016)) (Zhou et al., 2021). Exosomes can be produced by immune system

cells (Elashiry et al., 2021), epithelial cells (Han et al., 2017), tumor cells (Gu et al., 2012; Cheng et al., 2017; Ding et al., 2018; Chen et al., 2019; Hu and Hu, 2019; Amit et al., 2020; Jung et al., 2020; Yang et al., 2020) and CAFs (Herrera et al., 2018; Principe et al., 2018; Liu et al., 2020). CAFs are resident stromal cells of the TME; they have a promoting effect on carcinogenesis and progression of different neoplasms (Luga and Wrana, 2013; Huang et al., 2019; Sun and Fu, 2019) by transferring exosomes carrying ncRNAs to cells of the TME (Richards et al., 2017; Fiori et al., 2019) (Figure 1).

For everything mentioned above, the present work is based on the recent findings on the protumoral and antitumoral effects of CAFs-derived exosomal miRNAs and lncRNAs; it focuses on analyzing and highlighting the importance of these ncRNAs in the genesis and progression of different cancers. At the same time, it shows the current situation of this new growing research area, and a future perspective on the use of these ncRNAs as real therapeutic tools in the treatment of cancer patients is also proposed.

## EXOSOMES: INDUCING FACTOR IN THE FORMATION OF CAFs AND TUMOR MICROENVIRONMENT MODULATOR

Exosomes are among the most recognized inducers for generating CAFs (Li K. et al., 2020). CAFs are known as cells capable of secreting exosomes (You et al., 2019), and in turn, exosomes derived from cancer cells containing TGF-β can induce the generation of CAFs from stromal cells (Goulet et al., 2019). It has also been observed that exosomes derived from CAFs containing TGF-β activate the SMAD signaling pathway in cancer cells through a particular type of

epithelial-mesenchymal transition (EMT), which increases their malignant behavior (Li et al., 2017), thus generating a loop between CAFs and exosomes. It has been shown that chronic lymphocytic leukemia cells-derived exosomes can transfer miR-146a to bone marrow-derived mesenchymal stem cells to generate CAFs; this is done by promoting EMT by targeting ubiquitin specific peptidase 16 (*USP16*) (Yang et al., 2020). Another cellular transition process in which exosomes are involved to originate CAFs is the endothelial-mesenchymal transition; this event was demonstrated by observing that melanoma-derived exosomes loaded with TGF- $\beta$  induced the transition from human umbilical vein endothelial cells (HUVECs) to differentiated CAFs (Yeon et al., 2018). For their part, Baroni et al. demonstrated that triple-negative breast CAFs-derived exosomal miR-9 could generate a cell type with CAF-like properties in human breast fibroblasts, in which this miRNA enhanced the capacity for migration and invasion, as in breast cancer cell lines. Additionally, overexpression of this ncRNA in normal fibroblasts was able to promote tumor growth in a murine orthotopic xenograft model (Baroni et al., 2016).

It has also been observed that the exosomes produced by CAFs can modulate TME. For example, miR-21, which is packed in CAF-derived exosomes, induces the generation of monocytic myeloid-derived suppressor cells by activating STAT3 (Zhao et al., 2021). On a breast cancer model, exosomes produced by CAFs can also interfere with immunologic processes. In breast cancer cells treated with exosomes derived from CAFs, an increase of miR-92 was observed, which was essential for migration and invasion and correlated with the suppression of the immune cell function and the promotion of PD-L1 expression in these cells (Dou et al., 2020). Also, in the metastatic lung niche, a higher capacity to induce the transformation fibroblast into CAFs has been observed due to exosomal transport of miR-1247-3p from high-metastatic hepatocellular carcinoma cells; leading to a pro-inflammatory microenvironment promoted by CAFs, which secrete IL-6 and IL8, among other cytokines (Fang et al., 2018).

Considering this evidence, the important reciprocal relationship between exosomes and CAFs in the latter's self-generation and consequently in neoplasms' development is manifest. This relationship could be explored in greater depth and considered a previous or potentiating stage of carcinogenesis to inhibit the exosomal release and block exosomal molecules essential for the initiation, establishment, and progression of different cancers.

## CELLULAR EFFECTS OF CAFS-DERIVED EXOSOMAL MIRNAS AND LNCRNAs ON KEY EVENTS FOR GENESIS AND PROGRESSION OF NEOPLASMS

### Migration and Invasion, Processes Upregulated by CAFs-Derived Exosomal ncRNAs

Migration and invasion of cancer cells are essential for the establishment of the malignant neoplasm. Sun et al. isolated CAFs from patients with oral squamous cell carcinoma

(OSCC) and showed that in tongue squamous cell carcinoma CAL-27 cells, CAFs could promote these two events through the transfer of exosomal miR-382-5p, which facilitated the OSCC progression. Despite not having biologically determined the interaction, an analysis *in silico* predicted *PTEN*, *YBX1*, *RUNX1*, *STC1*, *JAM2*, and *MMP16* as candidate target genes for this miRNA (Sun et al., 2019). Another exosomal miRNA that has been shown to promote cell migration and invasion is miR-1228; this small non-coding regulatory RNA was enriched in exosomes secreted by CAFs and could downregulate endogenous *SCAI* mRNA and protein level in osteosarcoma, contributing to carcinogenesis of this neoplasm (Wang J.-W. et al., 2019).

CAFs-derived exosomes can also carry lncRNAs; LINC00659 is an example of this; it was found enriched in CAFs-derived exosomes and was shown to have multiple effects on human colorectal cancer (CRC) cells, it was able to induce cell proliferation, migration, invasion, and EMT *in vitro*. Furthermore, it was determined that these events were promoted by directly interacting with the tumor suppressor miR-342-3p to increase ANXA2 expression in CRC cells (Zhou et al., 2021).

The protumoral effects exerted by various CAFs-derived exosomal miRNAs and lncRNAs enhance the migration and invasion of cancer cells and convert them into key pieces within the universe of participants in developing neoplasms.

### CAFs-Derived Exosomal ncRNAs Promote Proliferation and Metastasis, Essential Malignant Characteristics for Tumor Progression

Among the multiple protumoral effects that CAFs-derived exosomal ncRNAs exert on cancer cells are the promotion of cell proliferation and metastasis. Chen et al. determined that CAFs isolated from samples of patients with invasive ductal carcinoma were capable of transferring exosomal miR-500a-5p to breast cancer cell lines, this miRNA bound to ubiquitin-specific peptidase 28 (*USP28*) promoting cell proliferation and metastasis in a nude mouse xenograft model (Chen et al., 2021). It has also been shown that miR-181d-5p can promote various protumoral cellular events in breast cancer cells, such as proliferation, invasion, and migration. If not enough, it can also induce EMT, antagonize apoptosis *in vitro* of breast cancer cells and promote tumor growth in nude mice xenografted with MCF-7 cells *via* downregulation of the transcription factors CDX2 and HOXA5 (Wang et al., 2020).

Another important effect carried out by CAFs exosomal ncRNAs is the reprogramming of metabolic pathways. Although to date, this aspect has not yet been studied in-depth, there is a report where a protumoral role is proposed for lncRNA SNHG3, which positively regulated pyruvate kinase isozymes M1/M2 (PKM) expression, inhibited mitochondrial oxidative phosphorylation, increased glycolysis, and proliferation of breast tumor cells through a mechanism similar to a molecular sponge for antitumoral miR-330-5p (Li Y. et al., 2020); this highlights the multifunctionality that CAFs-derived exosomal ncRNAs can exert on various processes related to carcinogenesis and tumor progression.

Considering the evidence reported, CAFs-derived exosomal miRNAs and lncRNAs can participate directly in tumor growth and the dissemination of cancer cells to other anatomical sites adjacent or far from the primary site, which could cause functional compromise of multiple organs and consequent serious complications in cancer patients.

## Treatment Resistance Generated by CAFs-Derived Exosomal miRNAs and lncRNAs

CAFs are an important factor in generating tumor resistance to treatment (Fiori et al., 2019); this protumoral feature is associated with worsening cancer patients' prognosis (Domvri et al., 2020; Huang et al., 2020). CAFs possess chemoresistance by innate nature and, it has been observed that in the presence of gemcitabine, a cytotoxic anticancer chemotherapy drug, they can transfer this characteristic to cancer cells. CAFs exposed to this antineoplastic drug could increase the release of miR-146a-loaded exosomes; in *in vitro* assays, this miRNA transmitted gemcitabine resistance to pancreatic cancer epithelial cell lines, promoting cell proliferation and survival. In the same work, it was shown that miR-146a is directly regulated by the promoter binding transcription factor, Snail, which acts as a chemoresistance-inducing factor, and that it was also found to be overexpressed in human pancreatic CAFs-derived exosomes (Richards et al., 2017). Recently, Gao et al. identified and characterized a subtype of CAFs which particularly has the presence of the cell surface protein CD63; these CD63<sup>+</sup> CAFs are capable of secreting exosomes enriched in miR-22, which can bind to their targets, *ERα* and *PTEN*, and deregulate their expression, thus conferring tamoxifen resistance to breast cancer cells (Gao et al., 2020).

Gemcitabine and tamoxifen are not the only drugs for which CAFs-derived exosomal miRNAs generate resistance in cancer cells; in fact, a considerable number of reports show that the cytotoxic effect caused by cisplatin in cancer cells can be diminished or eliminated by the action of CAFs-derived exosomal ncRNAs. It has been shown that, in cisplatin-sensitive ovarian cancer cells, CAFs-derived exosomal miR-98-5p was capable of binding to cyclin-dependent kinase inhibitor 1A (*CDKN1A*) to inhibit its expression, which increased ovarian cancer cell proliferation and cell cycle entry, suppressed cell apoptosis, and promoted cisplatin resistance *in vitro* and in a xenotransplanted nude mouse model (Guo et al., 2019). The intrinsic resistance that CAFs have towards cisplatin also favors the progression of head and neck cancer (HNC). It has been observed that CAFs can transfer exosomal miR-196a to HNC cells, which generated cell survival, proliferation, and inhibition of apoptosis, also conferred cisplatin resistance by targeting *CDKN1B* and *ING5*, cell cycle inhibitor and tumor suppressor molecules, respectively. Additionally, high levels of exosomal miR-196a in plasma were clinically correlated with poor overall survival and chemoresistance in patients with HNC (Qin et al., 2019).

There is a great diversity between the protumoral effects generated by CAFs-derived exosomal miRNAs and lncRNAs; it has been shown that miR-522 is capable of inhibiting ferroptosis, a novel mode of non-apoptotic cell death induced

by a build-up of toxic lipid peroxides (lipid-ROS) in an iron-dependent manner, in gastric cancer cells by targeting *ALOX15* and blocking lipid-ROS accumulation. Additionally, assays performed in an orthotopic implantation model in nude mice to evaluate gastric tumor growth and chemosensitivity led the authors to suggest that CAFs-derived exosomes containing miR-522 promote a new mechanism of acquired chemoresistance to cisplatin through an intercellular pathway, comprising USP7, hnRNPA1, miR-522, and *ALOX15* (Zhang H. et al., 2020).

On the other hand, it has been observed that miR-423-5p-loaded exosomes derived from CAFs can decrease the chemosensitivity of prostate cancer cells and increase the resistance of cells resistant to taxanes; in addition, it was shown that the inhibition of this miRNA enhanced the drug sensitivity of prostate cancer cells in a tumor xenograft model in nude mice. These protumoral events were favored due to the inhibitory effect of miR-423-5p on *GREM2* and the impact exerted on the TGF- $\beta$  pathway (Shan et al., 2020). In another type of neoplasm, in bladder cancer, it was found that miR-148b-3p can also induce resistance to treatment. Shan et al. validated *PTEN* as a target of miR-148b-3p; the negative dysregulation of *PTEN* promoted metastasis, EMT, and resistance to doxorubicin and paclitaxel both in *in vitro* assays using bladder cancer cells and in *in vivo* assays using a xenograft mouse model. These events were generated due to the tumor-promoting effects of miR-148b-3p *via* the Wnt/ $\beta$ -catenin pathway (Shan et al., 2021).

CAFs-derived exosomal miRNAs have also shown an inhibitory effect on the cytotoxic action that methotrexate exerts on the metabolism of colon cancer cells. In an *in vivo* model of colon cancer, it was shown that miR-24-3p induced resistance to this drug, favoring tumor growth under treatment of methotrexate by down-regulating the CDX2/HEPH axis (Zhang et al., 2021).

As mentioned previously, CAFs are also capable of secreting exosomal lncRNAs that promote tumor progression. Such is the case of exosomal lncUCA1, which conferred resistance to cisplatin in vulvar squamous cell carcinoma cells. Mechanistically, lncUCA1 functioned as a sponge for miR-103a, a miRNA with antitumoral function in various human cancers, this sequestration of miR-103a by lncUCA1 promoted the expression of WEE1 G2 checkpoint kinase (*WEE1*), a direct target of miR-103a, enhancing tumor growth and cisplatin resistance in a BALB/c nude xenograft model (Gao et al., 2021). Another CAFs-derived exosomal lncRNA with protumoral effect is H19, highly expressed in tumors generated in an azoxymethane (AOM)/dextran sodium sulfate (DSS) model of colitis-associated cancer, as well as in CRC samples from patients in different tumor-node-metastasis stages. Additionally, this lncRNA promoted the stemness of CRC stem cells, increased the frequency of tumor-initiating cells, and promoted the resistance of CRC cells to oxaliplatin both *in vitro* and *in vivo*. Mechanistically, H19 activated the  $\beta$ -catenin pathway by acting as an endogenous competitor for miR-141, a miRNA with antitumoral effect, in CRC cells (Ren et al., 2018).

These findings propose miRNAs and lncRNAs as important obstacles to achieving a successful chemotherapeutic treatment;

**TABLE 1 |** Cellular and tumor effects and mechanisms exerted by exosomal miRNAs and lncRNAs derived from CAFs in various cancers.

Exosomal ncRNAs Tumor effect	Cellular effects	Mechanisms	Cancer	References
miR-92 PRO-TUMOR	Promotes apoptosis and impairs proliferation of T cells, increases proliferation and migration of breast cancer cells, and facilitates tumor progression	Targets <i>LATS2</i> and modulates the LATS2-YAP1 axis generating an incremented expression of PD-L1	Breast	Dou et al. (2020)
miR-196a PRO-TUMOR	Promotes cell proliferation and confers cisplatin resistance	Targets and downregulates <i>CDKN1B</i> and <i>ING5</i>	Head and neck	Qin et al. (2019)
lncRNA LINC00659 PRO-TUMOR	Promotes cell proliferation, migration, invasion, and EMT progression	Interacts directly with miR-342-3p to increase ANXA2 expression	Colorectal	Zhou et al. (2021)
lncRNA-CAF PRO-TUMOR	Increases cell proliferation and promotes tumor growth	Stabilizes and up-regulates cytokine IL-33 to reprogram CAFs	Oral squamous cell	Ding et al. (2018)
miR-500a-5p PRO-TUMOR	Enhances cell proliferation and induces metastasis	Binds to tumor suppressor ubiquitin-specific peptidase 28 ( <i>USP28</i> )	Breast	Chen et al. (2021)
miR-181d-5p PRO-TUMOR	Induces cell proliferation, invasion, migration, and EMT, antagonizes apoptosis <i>in vitro</i> , and promotes tumor growth <i>in vivo</i>	Downregulates the expression of the transcription factors <i>CDX2</i> and <i>HOXA5</i>	Breast	Wang et al. (2020)
miR-423-5p PRO-TUMOR	Promotes chemotherapy resistance	Targets <i>GREM2</i> to inhibit its expression and favors the TGF- $\beta$ pathway	Prostate	Shan et al. (2020)
lncRNA UCA1 PRO-TUMOR	Enhances tumor growth and chemoresistance	Favors the expression of <i>WEE1</i> through sponging miR-103a	Vulvar squamous cell	Gao et al. (2021)
lncRNA H19 PRO-TUMOR	Promotes stemness and chemoresistance	Activates the $\beta$ -catenin pathway, acting as a competing endogenous RNA sponge for miR-141	Colorectal	Ren et al. (2018)
lncRNA SNHG3 PRO-TUMOR	Inhibits mitochondrial oxidative phosphorylation, increases glycolysis, and enhances cell proliferation	Functions as a molecular sponge of miR-330-5p to regulate the expression of <i>PKM</i>	Breast	Li et al. (2020b)
miR-148b ANTI-TUMOR	Inhibits EMT and reduces cell invasion and metastasis	Directly binds to <i>DNMT1</i> and decreases MMP-9 activity	Endometrial	Li et al. (2019)
miR-4516 ANTI-TUMOR	Suppresses cell proliferation	Targets <i>FOSL1</i> , proliferation-related gene	Breast	Kim et al. (2020)
miR-320a ANTI-TUMOR	Inhibits EMT, cell proliferation, migration, invasion, tumorigenesis, and metastasis	Binds to <i>PBX3</i> , suppresses the activation of the MAPK pathway, affects the expression of <i>CDK2</i> , and <i>MMP2</i> proteins due to reduced phosphorylation of <i>ERK1/2</i>	Hepatocellular	Zhang et al. (2017)
miR-3188 ANTI-TUMOR	Reduces cell proliferation, promotes apoptosis, and inhibits tumor growth	Directly targets <i>BCL2</i>	Head and neck	Wang et al. (2019b)
miR-34a-5p ANTI-TUMOR	Inhibits cell proliferation, migration, invasion, EMT, and tumorigenesis	Targets <i>AXL</i> , regulates the <i>AKT/GSK-3<math>\beta</math>/<math>\beta</math>-catenin/</i> Snail signaling cascade, and inhibits <i>MMP-2/9</i>	Oral	Li et al. (2018)

subject to further studies confirming this evidence, the elimination or reduction of CAFs-derived exosomal ncRNAs that generate chemoresistance should be considered as a new oncological therapeutic strategy.

### Exosomal miRNAs With Antitumoral Effects

miRNAs have generally been reported as protumoral molecules; however, some reports suggest that their silencing or elimination could favor tumor development. A feature shared between the antitumoral miRNAs is that they are significantly reduced in CAFs-derived exosomes. *In vitro* and *in vivo* studies carried out by Li et al. revealed that miR-148b could function as a tumor suppressor, the downregulation of this miRNA induced EMT, migration, invasion, and increased MMP-9 activity in endometrial cancer cell lines, as well as metastasis in a nude mouse model, additionally, DNA methyltransferase 1 (*DNMT1*) was determined as the target gene of miR-148b (Li et al., 2019). This enzyme has also been associated with tumorigenesis in breast cancer due to its indispensable role in the maintenance of mammary stem/progenitor cell and cancer stem cell maintenance (Pathania et al., 2015), and chemoresistance to cisplatin in human non-small cell lung cancer cell lines (Sui

et al., 2015). Another study also carried out in endometrial cancer showed that the CAFs-derived exosomal miR-320a inhibited the proliferation of cell lines by direct targeting and downregulation of hypoxia-inducible factor 1- $\alpha$  (*HIF $\alpha$* ) (Zhang N. et al., 2020). This transcription factor has been strongly related to metastasis, angiogenesis, poor patient prognosis, and tumor resistance therapy (Masoud and Li, 2015). In another neoplasm typical of women, the CAFs-derived exosomal miR-4516 was isolated from tumor tissue obtained from a patient with invasive breast ductal carcinoma; this miRNA suppressed the proliferation of breast cancer cell lines by targeting *FOSL1* (Kim et al., 2020).

The antitumoral effects that some miRNAs possess have not only been reported in gynecological cancers. *In vitro* and *in vivo* studies carried out in human hepatocellular carcinoma cell lines and in a nude mouse model, respectively, showed that miR-320a could function as an antitumoral miRNA, whose binding to *PBX3* affected the protein expression of cyclin-dependent kinase 2 (*CDK2*) and *MMP-2* due to the reduction of the phosphorylation of *ERK1/2*. In this way, the miR-320a/*PBX3* axis suppressed essential events for cancer progression such as EMT, cell proliferation, migration, invasion, tumorigenesis, and metastasis (Zhang et al., 2017). miR-3188 is another miRNA that

has an antitumoral effect; its loss of CAFs-derived exosomes contributed to the malignancy of HNC cells, increasing cell proliferation, migration, and invasion, and inhibited apoptosis by derepressing its target B-cell lymphoma 2 (*BCL2*) mRNA, this miRNA was also able to inhibit tumor growth in a BALB/c nude mice model (Wang X. et al., 2019).

Another of the few reports in which evidence is presented about the antitumoral effect of miRNAs is made by Li et al. It was observed that the overexpression of CAFs-derived exosomal miR-34a-5p suppressed the tumorigenesis of OSCC cells in an immunodeficient BALB/c mice subcutaneous tumor model. Additionally, in OSCC cell lines, it was shown that this miRNA is capable of binding directly to *AXL*, thus modulating the AKT/GSK-3 $\beta$ / $\beta$ -catenin signaling pathway; this event reduced proliferation, migration, and invasion, and decreased nuclear translocation of  $\beta$ -catenin, which led to decreased expression of Snail, a transcription factor of MMP-2 and MMP-9, important for EMT (Li et al., 2018).

Considering the reported evidence of some miRNAs' antitumoral effects in gynecological and non-gynecological cancers, these ncRNAs could become valuable tools to inhibit essential points in carcinogenesis and disease progression.

## CAFS-DERIVED EXOSOMAL MIRNAS AND LNCRNAs AS CANDIDATES FOR THERAPEUTIC TOOLS AND BIOMARKERS

Given the importance of protumoral and antitumoral miRNAs and lncRNAs in processes such as cell proliferation, migration, invasion, EMT, metastasis, metabolism, resistance to treatment (Table 1), these exosomal ncRNAs derived from CAFs have been suggested as strong candidates that could be used as new targets or therapeutic tools in breast, ovarian, vulvar squamous cell, endometrial, head and neck, pancreas, oral squamous cell, gastric, bladder, colon, liver, prostate cancer, as well as biomarkers of clinical relevance; CAFs-derived exosomal ncRNAs can be considered cornerstones in neoplastic processes.

## CONCLUSION AND PERSPECTIVES

Exosomes loaded with miRNAs and lncRNAs are a key communication pathway between CAFs and the different elements of the TME. Its relevance lies mainly in the promoter effect of protumoral and antitumoral events that modulate the genesis and the progression of various neoplasms. In the present work, the conventional effect of two types of exosomal ncRNAs derived from CAFs: miRNAs and lncRNAs, has been reviewed; this effect inhibits the translation by binding to its target mRNAs (Dragomir et al., 2018). Considering that cancer cells need different stimuli to form tumors and that CAFs, through the secretion of exosomal ncRNAs, among other mechanisms, can contribute significantly by favoring protumoral events, this type of extracellular vesicles derived from CAFs

loaded with miRNAs and lncRNAs can be considered as a potential therapeutic target to prevent the development of cancer. Nevertheless, despite the increase in the last 5 years of strong evidence suggesting CAFs-derived exosomal ncRNAs as therapeutic targets, more studies are needed to confirm the protumoral or antitumoral effects exerted by the various miRNAs and lncRNAs. Probably like miRNAs, lncRNAs have unconventional effects on gene expression that are still awaiting to be studied.

Regardless of future studies, the translational way from the laboratory to the clinic has begun. At present, an extensive database of ncRNAs in extracellular vesicles called EVAtlas, a product of enormous work, is available (Liu et al., 2021). In the site <http://bioinfo.life.hust.edu.cn/EVAtlas>, different characteristics such as extracellular vesicle types and isolation methods, expression level, functions, related drugs, and target genes of seven types of ncRNA of human extracellular vesicles can be consulted, as well as the pathological or physiological condition, tissues, cells, and biological fluids from which they have been isolated. This great bioinformatic tool could be part of the foundations to transfer the findings found *in vitro*, *ex vivo* and, *in silico* on the modulating effects of exosomal ncRNAs, derived and not derived from CAFs in the development of neoplasms, towards therapeutic regimens that improve the prognosis of cancer patients.

Although it is true that it will not be an easy task to incorporate miRNAs and lncRNAs as targets or tools in cancer treatment schemes, their relevance should not be underestimated. In the analysis carried out by GLOBOCAN (Ferlay et al., 2019; Ferlay et al., 2020), the global incidence and mortality rates of different cancers show an increase as the years go by, highlighting the need for additional options than those currently available to help in the fight against neoplasms. Designing and performing safe clinical trials, in which miRNAs and lncRNAs are used as therapeutic tools, is a great challenge and it will be essential to consider them a new real therapeutic alternative that benefits oncological patients.

## AUTHOR CONTRIBUTIONS

JV-P conceptualized and drafted the manuscript. ML-T designed the table and the figure. AR-d-A and AP-S critically reviewed the manuscript. AP-S led the activities. All authors approved the submitted version of the manuscript.

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