 doi:10.20944/preprints202207.0353.v1

Review

Cancer Stem Cells and Competing Endogenous RNAs

Hamid Aria[1,2], Mahdieh Azizi[2], Shima Nazem[3], Maryam Bahmanyar[4], Ali Moravej[5], Mohammad Hosein Pourjafarian[1], Babak Pezeshki[1], Alireza Tavassoli[6], Mohammad Kazem Vakil[1*†] and Yaser Mansoori[1,7*†]

1 Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran
2 Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
3 Department of Laboratory Medicine, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4 Pediatrics Department, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran
5 Department of Immunology, Fasa University of Medical Sciences, Fasa, Iran
6 Department of Pathology, Fasa University of Medical Sciences, Fasa, Iran
7 Department of Medical Genetics, Fasa University of Medical Sciences, Fasa, Iran
†These authors have contributed equally to this work and share correspondence
*Corresponding authors: mohammadkazemvakil.fums@gmail.com (M.K.V.); fums.mansoori@gmail.com (Y.M.)

Abstract: Cancer stem cells (CSCs) are one of the cell types that account for cancer heterogeneity. They arrest in the G0 phase and generate non-CSC progeny by self-renewing and pluripotency activity, resulting in tumor recurrence, metastasis, and chemoresistance. One CSC can stimulate tumor relapse and can re-grow a metastatic tumor. So, CSC is a promising target for eradicating tumors, and developing an anti-CSC method has become a top priority in cancer therapy. In recent years competing endogenous RNA (ceRNA) have emerged as an important class of post-transcriptional regulators that affect gene expression via competition for microRNA (miRNA) binding. Furthermore, aberrant ceRNA expression is associated with tumor progression. To overcome therapeutic resistance due to CSCs, we need to improve our existing understanding of the mechanisms by which ceRNAs are implicated in CSC-related relapse. Thus, this review was designed in order to discuss the role of ceRNAs in CSCs function. We reviewed the role of ceRNAs in acquiring CSCs characteristics in the form of different pathways including Rho GTPase/F-actin_ Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) (Hippo), Wnt/β-catenin pathway, transforming growth factor (TGF)-β–urothelial carcinoma-associated 1 (UCA1)–Slug pathway, etc. Finally, considering the comprehensive impacts of the ceRNA network on different pathways, a treatment strategy driving the ceRNA network might be effective. Targeting ceRNAs may open the path for new cancer therapeutic targets and can be used in clinical research.

Keywords: cancer stem cells; competing endogenous RNAs; ceRNA; lncRNA; micro-RNA; miRNA

1. Introduction

Despite substantial achievements in cancer research, there is still a lack of understanding of the basic mechanism of cancer development, demanding further research. While cancer begins with a single mutant cell, it is highly heterogeneous and includes a wide range of differentiated and proliferative cells. Tumor progression, recurrence, metastasis, and treatment resistance are thought to be caused by this heterogeneity (1). Among the various cell types that account for cancer heterogeneity, the presence of cancer stem cells (CSCs) is crucial (2). CSCs are a small number of tumorigenic cells inside the tumor mass that remain dominant during rapid tumor cell proliferation. They arrest in the G0 phase and generate non-CSC progeny by self-renewing and pluripotency activity, resulting in tumor recurrence, metastasis, and chemoresistance (3–5). CSCs possess some of the same markers (CD133 and CD44) as normal stem cells or signaling pathways involved in self-renewal and differentiate into different cell types (6–8). But CSCs are

 doi:10.20944/preprints202207.0353.v1

around 10-fold more tumorigenic than non-CSC populations, for example, in pancreas cancers (9).

2. CSCs, what is their importance?

CSCs are thought to be responsible for tumor growth with a low rate of proliferation, making them resistant to clinical chemotherapy and radiotherapy (10). Conventional therapies are effective in the early stages of cancer treatment, but they fail to target and eradicate CSCs, which contribute to chemoresistance and tumor recurrence (11). CSCs frequently express ATP-binding cassette (ABC) transporters, which are multidrug resistance proteins (MDRs) that export drugs from leukemia and some solid tumor cells and promote drug resistance (12). Chemotherapy and radiotherapy cause DNA damage and apoptosis, but CSCs, by increasing DNA repair capacities, can effectively prevent cancer cells from apoptosis (13). So, CSC is a promising target for eradicating malignant tumors; hence developing an anti-CSC method has become a top priority in cancer treatment.

CSCs are a scarce cell population within a tumor, but as the tumor progresses, this fraction can increase to over 30%, and this increase is associated with therapy resistance (14–18). Dysregulation of self-renewal is thought to be the first stage of tumorigenesis (19). Furthermore, CSCs have a critical role in epithelial-mesenchymal transition (EMT) and are thought to be the primary sources of tumorigenesis, development, metastasis, and relapse (20–24). Because CSCs have a high self-renewal potential, one CSC at the tumor site can stimulate tumor relapse and can re-grow a metastatic tumor at a distant location (15,25–27). As a result, tumors with a higher CSC marker have a weaker prognosis than tumors with a lower CSC population (28).

3. Non-coding RNAs and CSCs

The molecular mechanisms driving the development of CSC properties are currently unknown, but new research suggests that microRNAs (miRNAs) may play a role in CSC regulation (29). miRNAs are a type of non-coding RNA that has 19-22 nucleotides (30). They regulate gene expression through base pairing with its mRNA, inhibit translation, and increase mRNA degradation (31,32). miRNAs are involved in a variety of physiological and pathological processes, including tumorigenesis, metastasis, and therapy resistance (33–36). Tumor stage, metastasis, relapse, therapeutic resistance, and survival have all been associated with miRNA expression profiles (37,38). miRNAs have been associated with the modulation of CSC features such as cell-cycle progression, differentiation, migration, invasion, and EMT (39). As a result, studying miRNAs that impact drug sensitivity could be a valuable tool for getting a better understanding of the mechanisms behind drug resistance and cancer therapy.

RNA molecules with shared microRNA response elements (MREs) can regulate each other by competing for microRNA binding. This process is termed competing endogenous RNA (ceRNA) regulation (40). This theory suggests that there are interaction networks among all types of RNA transcripts through competing for identical sequences in miRNAs to modulate each other's expression (41,42). In recent years ceRNAs have emerged as an important class of post-transcriptional regulators that affect gene expression via competition for miRNAs binding (43). Extensive studies have found that aberrant ceRNA expression is associated with the progression, prognosis, and pathogenesis of cancers by modulating the expression of critical tumorigenic and tumor-suppressive genes (44,45).

Long non-coding RNAs (lncRNAs) are widely transcribed RNA molecules with more than 200 nucleotides but do not code for proteins (46). LncRNAs play a role in a variety of biological processes, including epigenetic regulation of gene expression, stem cell pluripotency regulation, and so on (47–49). Long intervening/intergenic non-coding RNAs (Linc-RNAs), intronic ncRNAs, and sense or antisense lncRNAs are all types of lncRNAs that have various genomic locations in regard to genes and exons (50). Through competitive miRNA binding, lncRNAs act as the key regulatory mechanisms affecting many targeted genes.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2022 doi:10.20944/preprints202207.0353.v1

To overcome therapeutic resistance, we need to improve our existing understanding of the mechanisms by which ceRNAs are implicated in CSC-related relapse. Thus, this review was designed in order to discuss the role of ceRNAs in CSCs function (Table 1).

Table 1. ceRNA regulation network related to cancer stem cell (CSC) properties.

lncRNA	miRNA	mRNA	Cancer type	Effect in CSC	Ref.
Linc-RNA-ROR	miR-205	*ZEB1, ZEB2, ErbB3 and VEGF-A*	Breast cancer	Maintaining the stem cell properties	(53)
Linc-RNA-ROR	Members of let-7 family miR-93-5p miR-145-3p miR-320a miR-320b	-	Pancreatic ductal adeno-carcinoma	Maintaining the stem cell properties	(55)
Linc-RNA-ROR	miR-145	*OCT4, SOX2, and NANOG*	-	Maintaining the stem cell properties	(62)
Linc-RNA-ROR	miR-145	*OCT4*	Prostate cancer	Maintaining the stem cell properties	(64)
Linc-RNA-ROR	miR-145	*OCT4, SOX2, and NANOG*	Colon cancer	Maintaining the stem cell properties and drug re-sistance	(68)
OCT4B	miR-145 miR-335 miR-20a miR-20b miR-106a miR-106b	*OCT4A*	Colorectal cancer	Maintaining the stem cell properties	(71)
STARD13-correlated ceRNA network	miR-424 miR-374a miR-590-3p miR-448 miR-15a	*LATS1/2*	Breast cancer	Suppressing the stem cell development	(82)
MALAT1	miR-375	*YAP1*	Liver cancer	Maintaining the stem cell properties	(87)
CD44	miR-34a-5p miR-373-3p miR-520c-3p	*ULBP2*	Liver cancer	NK sensitivity of cancer stem	(109)
GAS5	miR-196a-5p	*FOXO1*	Glioma	Suppressing the stem cell development	(117)
UCA1	miR-1 miR-203a	*Slug*	Glioma	Induced stemness	(125)
LINC00657	miR-203a	*ZEB1, ZEB2, and Snail2*	Colorectal cancer	Promotes stem-like cell in-vasion	(134)
H19	miR-let7	*LIN28*	Breast cancer	Maintaining the stem cell properties	(139)
HOTAIR	miR-211-5p	*FLT-1*	Colorectal cancer	Maintaining the stem cell properties	(149)
C8orf34-as1	miR-671-5p	*MFAP4*	Lung adenocarcinoma	Suppressing the stem cell development	(153)
MEG3	miR-708	*SOCS3*	Colorectal cancer	Suppressing the stem cell development	(150)
MEG3	miR-650	*SLC34A2*	Non-small cell lung can-cer	Suppressing the stem cell development	(151)

 doi:10.20944/preprints202207.0353.v1

E2F6	miR-193a	*c-KIT*	Ovarian cancer	Maintaining the stem cell properties and drug resistance	(152)
MYOSLID: 11	miR-149-3p	*PXN*	Glioblastoma	Maintaining the stem cell properties	(158)

4. CSC and Linc-RNA-ROR_miR-145_OCT4 pathway

Because lincRNA feedback loops influence the fundamental pluripotency factors octamer-binding transcription factor 4 (*OCT4*), SRY [sex-determining region Y]-box 2 (*SOX2*), and *C-MYC*, it's possible that lincRNA is involved in sustaining cancer stem cell characteristics (51,52). *Linc-RNA-ROR* is a typical lncRNA that has been involved in supporting stem cell pluripotency as well as tumor progression in earlier research (53,54). Extracellular vesicle-mediated transfer of *Linc-RNA-ROR* inhibits the sensitivity of $CD133^{+}$ liver CSCs to chemotherapeutic treatments by regulating transforming growth factor (*TGF*) expression (54). In vitro, *Linc-RNA-ROR* knockdown reduced pancreatic cancer cell proliferation, colony-forming ability, and invasion and impaired pancreatic cancer cell stem-like properties (55).

Hou et al. reported that *Linc-RNA-ROR* promotes EMT in breast cancer cells via sponge miR-205 (53). Moreover, *Linc-RNA-ROR* was revealed as an endogenous sponge that inhibited embryonic stem cell (ESCs) differentiation by binding to miR-145, leading to maintaining ESC self-renewal (56). In most cancers, miR-145 is downregulated (57–59). Given that many ESC-related genes are found in CSCs, it's reasonable to assume that *Linc-RNA-ROR* has a role in modulating CSC features (60,61).

Since *Linc-RNA-ROR* has been proven to play an important function in maintaining the pluripotency of human ESC and compliance with its role in induced pluripotent stem (iPS) cells, Fu et al. discovered that *Linc-RNA-ROR* expression correlates to stemness in pancreatic cancer cells (55). Their findings revealed that silencing *Linc-RNA-ROR* inhibited sphere formation, CSC marker expression, and carcinogenesis. By comparing microarray data, they discovered numerous CSC inhibitory miRNAs, including several members of the let-7 family, miR-93-5p, miR-320a, miR-320b, and miR-145'3p, were increased in *Linc-RNA-ROR* transcript (55). Notably, *Linc-RNA-ROR* demonstrated potential ceRNA activity targeting other tumor-suppressor miRNAs, including, miR-205, miR-181a, miR-99b, and let-7a-5p (53,62), reducing its effective concentration (53,56,62), and protect core transcription factors in CSCs (63).

The expression of *Linc-RNA-ROR* was found to be significantly associated with human prostate CSCs proliferation, while the expression of miR-145 was found to be adversely associated with prostate CSCs proliferation. Liu et al. found that curcumin inhibits prostate CSCs proliferation, invasion, and tumorigenicity through ceRNA actions of miR-145 and *Linc-RNA-ROR* (64). *OCT4* is a transcription factor that is expressed in a variety of cancers and maintains the proliferation and pluripotency (stemness) of CSCs (65–67). *OCT4* and *Linc-RNA-ROR* are both suppressed by miR-145. In prostate CSCs, decreasing the expression of endogenous *Linc-RNA-ROR* substantially increased the concentration of miR-145, whereas miR-145 inhibits cell proliferation via reducing *OCT4* expression. The expression of *OCT4* and *Linc-RNA-ROR* was balanced, allowing prostate CSCs to maintain the expression of cell cycle kinases and progress through the cell cycle, increasing their proliferation and invasion (64).

The function of *Linc-RNA-ROR* as a ceRNA that upregulates *OCT4*, *SOX2*, and *NANOG* expression by sponging miR-145 was also reported by Yan ZY et al. Their results have shown that miR-145 can inhibit the expression of *Linc-RNA-ROR*, *OCT4*, *SOX2*, and *NANOG*. In contrast, *Linc-RNA-ROR* via sponging this miRNA significantly increased colon CSC proliferation and decreased the sensitivity to chemotherapy (68) (Figure 1). The human *OCT4* gene can generate three mRNA isoforms (*OCT4A*, *OCT4B*, and *OCT4B1*) by alternative splicing (69). *OCT4B* is introduced as a non-coding RNA among spliced isoforms, modulating *OCT4A* expression in a miRNA-dependent manner (ceRNA

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2022 doi:10.20944/preprints202207.0353.v1

regulation). The *OCT4* protein, notably the *OCT4B* isoforms, is expressed at low levels in most cancers (70). Li et al. have shown that manipulating *OCT4B* expression may alter cell proliferation based on its impact on *OCT4A* via competitive binding with miRNAs. In their study, overexpression of miR-145, miR-335, miR-20a, miR-20b, miR-106a, and miR-106b caused a significant downregulation of OCT4 protein in the HCT116 cells, which inhibited cell proliferation. So, *OCT4B* controls *OCT4A* expression as anti-apoptotic ceRNA in tumor cells (71).

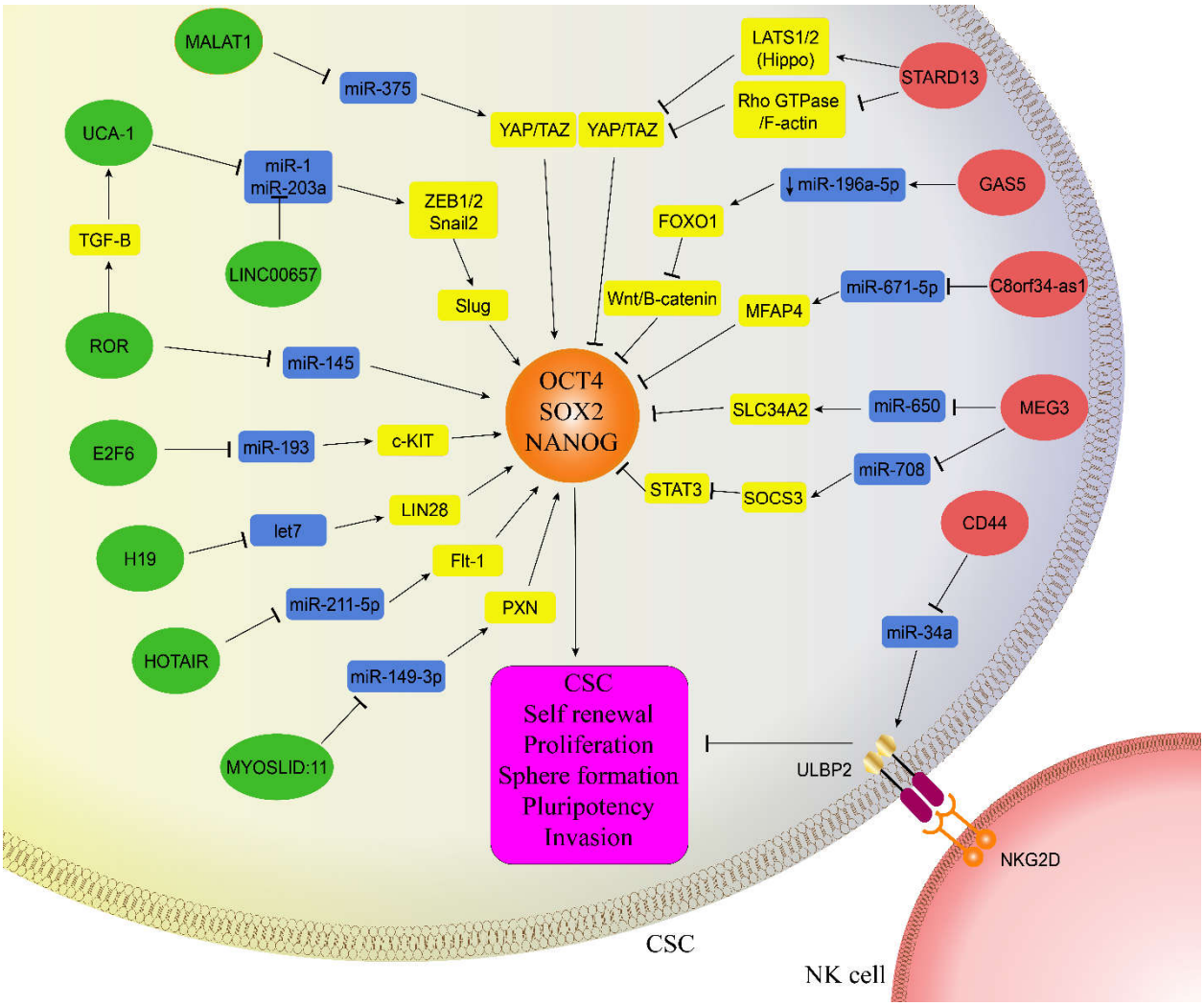

Figure 1. ceRNAs and their pathways that play a role in the acquisition of CSC characteristics. ceRNAs in red are inhibitory and in green are CSC promoters.

5. CSC and Rho GTPase/F-actin_YAP/TAZ (Hippo) pathway

Yes-associated protein (YAP)/ transcriptional co-activator with PDZ-binding motif (TAZ), which mediates the crucial role in the Hippo pathway, are known to be stemness factors in the formation of breast CSCs (72). YAP1 has been associated with cancer cell proliferation, EMT, chemoresistance, and suppresses cell apoptosis (73). Upregulation of YAP1 may result in CSC characteristics such as sphere formation and self-renewal (74,75). The role of YAP1 in acquiring CSC characteristics is mediated by the upregulation of ESC factors such as *OCT4*, *SOX2*, and *NANOG* (76,77). Also, TAZ was found to induce CSC-like characteristics on breast cancer cells in a previous study, and in numerous types of stem cells, YAP/TAZ are referred to as "stemness factors" (78). Furthermore, actin remodeling factors could regulate YAP/TAZ activity (79).

 doi:10.20944/preprints202207.0353.v1

The Hippo signaling pathway is a kinase cascade including mammalian STE20-like protein kinase 1 (MST1) and large tumor suppressor 1/2 (LATS1/2), which is critical for cell proliferation, death, and organ growth modulation (80,81). As essential members of the Hippo pathway, LATS1/2 could phosphorylate and inactivate the downstream effectors, YAP/TAZ.

Furthermore, StAR-related lipid transfer domain protein 13 (STARD13), cadherin 5 (CDH5), homeobox D1 (HOXD1), and HOXD10 (termed the STARD13-correlated ceRNA network) have been identified as deterministic upstream controller of YAP/TAZ transcriptional activity. The STARD13-correlated ceRNA network was able to co-regulate each other by competing for numerous shared miRNA binding sites, resulting in the formation of a ceRNA network to suppress breast cancer EMT and metastasis coordinately (82). Zheng et al. found that the STARD13-related ceRNA network inhibited the development of breast CSCs. The STARD13-correlated ceRNA network enhanced LATS1/2 activity, indicating that this ceRNA network plays a role in regulating the Hippo pathway. Notably, CDH5-, HOXD1-, and HOXD10-3′ untranslated region (UTRs) could not act in this pathway without STARD13, implying that STARD13 played an essential role in bridging CDH5, HOXD1, and HOXD10 with LATS1/2 (Hippo cascade). In line with this, the lack of LATS1/2 reduced the inhibitory effects of the STARD13-correlated ceRNA network on CSC and EMT features, indicating that the tumor-suppressive effects of the STARD13-correlated ceRNA network are mediated by LATS1/2 modulation (82).

Human ESC expansion and long-term survival may be facilitated by Rho GTPase/F-actin signaling (83). On the other hand, STARD13 may act as a Rho GTPase activating protein (GAP) that inhibits Rho GTPases and thus RhoA activity, causing the cytoskeleton to reorganize (84,85). Rho GTPase and F-actin rearrangements are essential for YAP/TAZ activity, according to previous research (79,86). Mechanotransduction is intricately linked with cytoskeletal dynamics, and YAP/TAZ responds to mechanical stimuli from the surrounding extracellular matrix, which alerts cells of the need to preserve stem cell properties (74). By suppressing Rho GTPase/F-actin signaling, the STARD13-correlated ceRNA network could also regulate YAP/TAZ activity.

The STARD13-correlated ceRNA network might suppress breast CSC characteristics via two different routes (LATS1/2 and RhoA/F-actin signaling), both of which resulted in YAP/TAZ translocation from the nucleus to the cytoplasm. Their findings attempt to establish novel cooperation and coordination between oncogenic Rho GTPase/F-actin function and the tumor-suppressive LATS1/2 (Hippo pathway) as two synergistic components of the STARD13-correlated ceRNA in modulating breast CSC characteristics. To summarize, STARD13, which is triggered by CDH5, HOXD1, and HOXD10 ceRNAs, stimulates Hippo signaling by acting as a ceRNA for upregulating the LATS1/2 and blocks the Rho GTPase/F-actin pathway, inhibiting YAP/TAZ and suppressing EMT and CSC development in breast cancer (82) (Figure 1). They predicted that verteporfin, a YAP-TEAD binding inhibitor, may be utilized in combination with other treatments to target breast CSCs. It was found that the ceRNA function of STARD13 3′UTR on LATS1/2 is achieved by targeting other miRNAs, including miR-424, miR-374a, miR-5903p, miR-448, and miR-15a.

In another study, metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is introduced as highly conserved lncRNAs, which could maintain the stemness of liver CSCs by upregulating YAP1 via sponging miR-375 (87) (Figure 1). *MALAT1* was upregulated in different cancers and has been associated with tumor progression, invasion, and chemoresistance (88–91). Also, it has been correlated with CSC characteristics (sphere formation and the upregulation of stemness markers) of pancreatic cancer, osteosarcoma, and glioma (92–94). *MALAT1* knockdown in pancreatic cancer cells inhibited the sphere formation and the expression of self-renewal related factors, including *SOX2*, implying that *MALAT1* may increase pancreatic CSC stemness characteristics by upregulating *SOX2* expression (92). Zhao et al. have shown that knockdown of *MALAT1* with small interfering RNA (siRNA) cause reduced expression of *YAP1*, whereas the inhibition of miR-375 can induce *YAP1* overexpression (87).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2022 doi:10.20944/preprints202207.0353.v1

MiR-375 was thought to be a multifunctional pancreatic islet-specific miRNA that modulates pancreatic islet development, glucose homeostasis, insulin secretion, mucosal immunity, and carcinogenesis (95). miR-375 levels were previously found to be significantly lower in a variety of cancers, including liver cancer, and have been associated with poor survival (96,97). By targeting numerous key oncogenes, such as janus kinase 2 (*JAK2*), receptor tyrosine-protein kinase erbB-2 (*ERBB2*), astrocyte elevated gene-1 (*AEG-1*), and autophagy-related 7 (*ATG7*), miR-375 could inhibit liver cancer cell proliferation and migration while also circumventing drug resistance (98–101). It could be used as a predictive biomarker for disease progression in hepatocellular carcinoma (97). YAP1 was identified as a target of miR-375. *MALAT1*, by acting as a ceRNA for miR-375, promotes liver CSC properties through the post-transcriptional regulation of *YAP1* expression (87).

6. CSC and CD44/NK cell activation

CD44, a transmembrane glycoprotein, is involved in a wide range of physiological processes, including cell adhesion, lymphocyte activation, cell migration, cell proliferation, angiogenesis, and tumor metastasis (102). In the liver, gastric, or breast cancer, and acute myeloid leukemia (AML), CD44 is a CSC marker (103). Also, prostate CSCs have a $CD44^{+}/\alpha2\beta1^{high}/CD133^{+}$ phenotype and constitute about 0.1 percent of the prostate cancer cells. In comparison to $CD44^{-}/\alpha2\beta1^{low}/CD133^{-}$ cells, CSCs have a greater capacity for proliferation and invasion (23,104). In comparison to $CD44^{-}/CD133^{-}$ cells, the Notch pathway was active in prostate CSCs, in addition to high expression of stem cell markers such as *SOX2*, *CMYC*, *OCT4*, krüppel-like factor 4 (KLF4), CD90, and stage-specific embryonic antigen-1 (SSEA-1) (105).

Cell proliferation and colony formation are inhibited by CD44's non-coding 3'-UTR, whereas cell adhesion, motility, and invasion are enhanced. CD44 modulates the expression of CDC42, a Rho GTPase involved in cell motility and cell-cycle progression, by binding and sequestering miR-216a, miR-330, and miR-608 (106).

UL16 binding protein 2 (ULBP2) is expressed on cancer cells and binds to natural killer (NK) cell activating ligand, NKG2D, increasing cancer cell sensitivity to NK cell-mediated cytotoxicity (107). Contrary to most of the previous studies that the tumor-suppressive roles of miR-34a have been mentioned (108,109) (Figure 1), Anja Heinemann et al., revealed that miR-34a and miR-34c are adversely related to surface ULBP2, sensitize tumor cells to kill by NK cell (110). Since ULBP2 is a receptor of miR-34a, CD44 interferes with miR-34a's binding and increases the expression of *ULBP2* in liver CSCs, which causes NK cells to kill the CSCs. CD44 protected ULBP2 in a ceRNA mechanism, primarily by binding miR-34a specifically to prevent ULBP2 degradation (111). miR-34a, being a tumor-suppressive miRNA, has a relatively low concentration, which is ideal for forming the ceRNA network. Their findings suggested that CD44 could act as a ceRNA to regulate *ULBP2* expression by competing with miR-34a, miR-373, and miR-520c, expanding the ceRNA function of CD44 3′UTR in ULBP2 modulation. As a result, anti-CD44 antibody had no effect on NK cell-mediated cytotoxicity in liver CSCs, which could be considered a possible approach to eliminating liver CSCs.

7. CSC and Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway, which affects the production of various CSC-related miRNAs such as miR-34, miR-302, and let-7, was found to be inhibited by miR-320 (112–115). According to studies, lncRNA growth arrest-specific transcript 5 (GAS5) can inhibit the activation of the Wnt/β-catenin signaling pathway, thereby suppressing angiogenesis, invasion, and metastasis in various tumors. In a study, Li et al. revealed that GAS5, as a ceRNA, can decrease triple-negative breast cancer (TNBC) cell progression by competitively binding to miR-196a-5p (116). The role of GAS5 as ceRNA in CSCs also demonstrated by Zhao et al. MiR-196a-5p via downregulation of the forkhead box protein O1 (FOXO1) expression stimulates glioma stem cell (GSC) proliferation, migration, and invasion (117) (Figure 1). Their data showed that GAS5 exerted tumor suppressive

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2022 doi:10.20944/preprints202207.0353.v1

functions in glioma stem cells via sponging miR-196a-5p, thus resulting in attenuation of tumor migration and invasion activities. Using gene microarray, another study reported that miR-105/93-3p promotes stemness, chemoresistance, and TNBC cell metastasis via activating Wnt/β-catenin signaling. The activation of this pathway induces through the downregulation of secreted frizzled-related protein 1 (SFRP1) because SFRP1 is most sensitive to miR-93-3p upregulation (44).

8. TGF-β–UCA1–Slug pathway

LncRNA urothelial carcinoma-associated 1 (UCA1) has been found to stimulate the proliferation, migration, and invasion of cervical cancer cells or glioma cells by modulating the expression of miR-206, miR-122, and miR-182 (118–120). By upregulating zinc finger E-box binding homeobox 1 (ZEB1), UCA1 could sponge miR-204-5p to stimulate glioma cell motility, invasion, and EMT (121). According to the He et al. study, UCA1 regulates glycolysis that is conducted by glioblastoma stromal cells and glioma cell invasion (122). TGF-β, a significant EMT activator, accelerates the invasion and metastasis of non-small cell lung cancer (NSCLC) and enhance the stemness of MiaPaCa-2 pancreatic cancer cell (123,124). According to Li et al., TGF-β triggered the UCA1 expression in glioma cells (125) (Figure 1). Moreover, TGF-β promoted EMT and stemness, whereas UCA1 knockdown inhibited this action. They also found that UCA1 acted as a ceRNA by competitively binding to miR-1 and miR-203a, increasing the expression of Slug, a downstream effector of TGF-β signaling pathway. In a variety of cancers, including colorectal, renal, lung, esophageal, and head and neck cancer, miR-203a functions as a tumor suppressor gene and inhibits invasion by suppressing its target genes, including ZEB1, ZEB2, and Snail2 expression (126–132). Overexpressing Slug reversed the effects of UCA1 knockdown on glioma cell EMT and stemness, and their expression showed a positive association in glioma tissues. These findings imply that UCA1 plays a crucial role in the regulation of EMT, stemness, and drug resistance, suggesting that it may be a promising target for glioma therapy.

Previous research suggested that LINC00657 may function as an oncogene in the colon and gastric cancer (131,133). High LINC00657 expression in CRC was correlated to metastasis, poor survival, and advanced clinical stage. According to Zhao et al. findings, LINC00657 was increased in human colorectal cancer cells and CSCs (134). In vitro CSC invasion was inhibited by LINC00657 knockdown. Furthermore, LINC00657 functioned as a miR-203a competing endogenous RNA, counteracting its activity as a tumor suppressor gene and causing the CSC invasion. After transfection with si-LINC00657, the expression of ZEB1, ZEB2, and Snail2 was downregulated in CSCs; however, their expression was reversed after transfection with si-LINC00657 plus miR-203a inhibitor. By interacting with miR-203a, which targets ZEB1, ZEB2, and Snail2, LINC00657 boosted CSCs invasion (Figure 1).

9. Other pathways

LncRNA *H19* seems to be implicated in proliferation, differentiation, EMT, and stemness, implying that it plays a role in tumorigenesis and progression (135,136). *H19* has recently been demonstrated to repress the *P53* protein, implying that *H19* plays a role in carcinogenesis (137). At the time of implantation, *H19* is activated in extraembryonic cells; however, after birth, its expression in all tissues significantly declines (138). *H19* enhances sphere-forming capacity while its deletion decreases colony-forming ability (139). *H19* acts as an endogenous sponge for the tumor suppressor let-7 to regulate cancer metastasis (140) (Figure 1). Compared to surrounding tissues, let-7 expression is lower in breast tumor tissues. On the other hand, *H19* overexpression or reduction did not affect cell proliferation in breast cancer cells, implying that *H19*-regulated spheroid formation, colony formation, and tumor-initiating activities are correlated to self-renewal. The stemness maintenance of breast CSCs via sponging the tumor suppressor let7 miRNA is one of the ceRNA activities of *H19* lncRNA. In this line, Peng et al. found that *H19* is overexpressed

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2022 doi:10.20944/preprints202207.0353.v1

in breast cancer cells and, by acting as a ceRNA to inhibit the synthesis of miR-let7, promotes the expression of LIN28 mRNA, the core RNA-binding pluripotency stem cell factor implicated in breast CSCs maintenance (141). Indeed, *H19* protects LIN28 from let-7-mediated degradation. In adult human fibroblast cells, the RNA-binding protein LIN28 collaborated with KLF4, SOX2, and NANOG to promote pluripotency (142,143). In advanced human cancers, LIN28 is overexpressed and promotes cancer growth and metastasis by upregulating LGR5 and PROM1. It plays a crucial function in the development of CSCs (144,145). Pre-let-7 elements have a conserved terminal loop that LIN28A binds to it. The LIN28 blocking let-7 synthesis and repressed let-7 miRNA target genes (RAS, MYC, and high mobility group AT-Hook 2 [HMGA2]), which is critical for CSC maintenance (146–148). Furthermore, via a feedback loop, LIN28 induction can diminish let-7 expression even further, as well as *H19* is repressed by let-7. Surprisingly, increased *H19* expression significantly boosted breast CSCs characteristics such as self-renewal, colony formation, sphere-forming capacity, and migration (141).

HOX transcript antisense RNA (*HOTAIR*) is another lncRNA that acts as ceRNA and promotes CSC properties in colorectal cancer. This lncRNA can facilitate the expression of Fms-like tyrosine kinase-1 (Flt-1) via downregulating miR-211-5p expression and activity (Figure 1). Flt-1 is the type 1 receptor for vascular endothelial growth factor A (VEGF-A), and a CSC marker for CSC cells in colorectal cancer, which increase its expression and cause tumor initiation, progression, migration, and metastasis (149).

Maternally expressed gene 3 (*MEG3*), is a lncRNA that acts as a tumor suppressor in multiple cancers. According to a variety of studies, *MEG3* is involved in the regulation of cell proliferation, migration, invasion, and chemoresistance through the "sponging" of mRNAs or miRNAs, and its depletion is reported to enhance stem-cell-like properties in a variety of cell types, including germline stem cells, mesenchymal stem cells, and lung cancer cells. In a study, S. Zhang et al. introduced *MEG3* as a ceRNA that prevents the proliferation of colonic stem cells (150). Their results showed that *MEG3* sponges miR-708 to enhance expression of suppressor of cytokine signaling 3 (*SOCS3*) and suppress signal transducer and activator of transcription 3 (STAT3) signaling and malignant proliferation of colonic stem cells during the early stage of colon tumor formation. The role of *MEG3* as a ceRNA also was reported in lung cancer stem cells (LCSCs). Upregulation of *MEG3* promotes the protein level of solute carrier family 34 member 2 (*SLC34A2*) and curbs migration and invasion in LCCs and LCSCs by sponging miR-650 (151) (Figure 1). The inhibition of *SLC34A2* restored cell migration and invasion, which was prevented by miR-650 downregulation. So, *MEG3* as a ceRNA plays an important role in the stem cell-like state of LCCs and inhibits migration and invasion in NSCLC via the miR-650/SLC34A2 axis.

The involvement of ceRNA networks in tumor progression and stemness was reported in ovarian cancer by Cheng et al. (152). E2F transcription factor 6 (E2F6) is upregulated in ovarian cancer when estrogen (E2) binds to the estrogen receptor (ER). Upregulated *E2F6* mRNA, in turn, upregulates the oncogene *c- KIT*, a facilitator of cancer "stemness". Overall, *E2F6* via competitive inhibition of miR-193 binding acts as a ceRNA to increase the expression of the *c-KIT*, thus advancing tumor progression (Figure 1).

Identified differentially expressed lncRNAs (DElncRNAs), DEmiRNAs, and DEmRNAs between cancer and normal tissues using the cohort from the TCGA data set also introduced new ceRNA networks correlated with CSC. Han et al. found a novel cancer stemness-related ceRNA axis (*C8orf34-as1*/miR-671-5p/MFAP4) in lung adenocarcinoma (LUAD) via multiple bioinformatics analyses (153) (Figure 1). Microfibrillar-associated protein 4 (*MFAP4*) is an extracellular glycoprotein that may be involved in cell adhesive activity (154), and dysregulation of this protein is reported in a variety of malignant tumors (155). In prostate and urinary bladder cancer, MFAP4 acts as a tumor suppressor (156,157), and by targeting *MFAP4*, miR-147b increased aggressiveness in LUAD cells (158). Low expression of *MFAP4* was associated with LUAD patients' poor prognosis. Also, it was revealed that lncRNA *C8orf34-as1* is correlated to the prognosis of LUAD patients (159). The results of Han et al. have shown that the *C8orf34-as1* acts as an endogenous sponge by binding to miR-671-5p and abolishing miRNA-induced MFAP4

 doi:10.20944/preprints202207.0353.v1

suppression. This ceRNA regulatory axis correlates with the cell invasion and stemness of LUAD (153).

Another study used TCGA to incorporate the ceRNA network into the GSC differentiation process. Zhao et al. identified lncRNA *MYOSLID: 11* as a ceRNA that regulated the expression of the downstream gene paxillin (*PXN*) by competitively binding with hsa-miR-149-3p in GSC (Figure 1). The increased expression of *PXN* strikingly increases tumor cell and stem cell migration and invasion (160).

10. Discussion

As a result, considering the comprehensive impacts of the ceRNA network on different pathways, a treatment strategy driving the ceRNA network might be proposed. On the other hand, further therapies targeting CSCs for cancer treatment are urgently needed, particularly for that whit a poorly differentiated "stem/progenitor" cell phenotype. The successful development of novel treatment strategies that target CSCs has the potential to improve cancer patient outcomes.

Due to the diversity of miRNA targets, other non-coding RNAs may act as ceRNAs to modulate important gene expression in CSCs. The identification of these ceRNAs could assist the researcher in better understanding tumorigenesis. These findings and targeting this recently discovered regulatory circuitry may open the path for discovering new cancer therapeutic targets and shed light on the understanding of novel predictive biomarkers that can be used to guide clinical research.

Author Contributions: All authors contributed to the study's conception and design. Review and editing were performed by M.B., A.M., M.P., B.P., and A.T. Visualization was performed by S.N., and the project was supervised by M.V. and Y.M. The first draft of the manuscript was written by H.A. and M.A., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding: This research received no external funding.

Consent for publication: This manuscript has not been previously published and is not under consideration for publication elsewhere.

Conflicts of Interest: The authors declare no conflict of interest.

List of abbreviations:

Cancer stem cells (CSCs),
multidrug resistance proteins (MDRs),
ATP-binding cassette (ABC),
epithelial-mesenchymal transition (EMT),
microRNAs (miRNAs),
competing endogenous RNA (ceRNA),
long non-coding RNAs (lncRNAs),
long intervening/intergenic non-coding RNAs (Linc-RNAs),
transforming growth factor (TGF),
embryonic stem cell (ESCs),
octamer-binding transcription factor 4 (OCT4),
SRY [sex-determining region Y]-box 2 (SOX2),
yes-associated protein (YAP),
transcriptional co-activator with PDZ-binding motif (TAZ),
mammalian STE20-like protein kinase 1 (MST1),
large tumor suppressor 1/2 (LATS1/2),
StAR-related lipid transfer domain protein 13 (STARD13),
cadherin 5 (CDH5),
homeobox D1 (HOXD1),
untranslated region (UTRs),
GTPase activating protein (GAP),

metastasis-associated lung adenocarcinoma transcript 1 (MALAT1),
small interfering RNA (siRNA),
as janus kinase 2 (JAK2),
receptor tyrosine-protein kinase erbB-2 (ERBB2),
astrocyte elevated gene-1 (AEG-1),
autophagy-related 7 (ATG7),
acute myeloid leukemia (AML),
krüppel-like factor 4 (KLF4),
stage-specific embryonic antigen-1 (SSEA-1),
UL16 binding protein 2 (ULBP2),
growth arrest-specific transcript 5 (GAS5),
triple-negative breast cancer (TNBC),
forkhead box protein O1 (FOXO1),
glioma stem cell (GSC),
secreted frizzled-related protein 1 (SFRP1),
zinc finger E-box binding homeobox 1 (ZEB1),
non-small cell lung cancer (NSCLC),
HOX transcript antisense RNA (HOTAIR),
Fms-like tyrosine kinase-1 (Flt-1),
vascular endothelial growth factor A (VEGF-A),
maternally expressed gene 3 (MEG3),
suppressor of cytokine signaling 3 (SOCS3),
signal transducer and activator of transcription 3 (STAT3),
lung cancer stem cells (LCSCs),
solute carrier family 34 member 2 (SLC34A2),
E2F transcription factor 6 (E2F6),
differentially expressed lncRNAs (DElncRNAs),
lung adenocarcinoma (LUAD),
paxillin (PXN),
high mobility group AT-Hook 2 (HMGA2),
urothelial carcinoma-associated 1 (UCA1).

References

1. Khan AQ, Ahmed EI, Elareer NR, Junejo K, Steinhoff M, Uddin S. Role of miRNA-regulated cancer stem cells in the pathogenesis of human malignancies. Cells. 2019;8(8):840.
2. Nassar D, Blanpain C. Cancer stem cells: basic concepts and therapeutic implications. Annu Rev Pathol Mech Dis. 2016;11:47–76.
3. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev cancer. 2008;8(10):755–68.
4. Yang M, Liu P, Huang P. Cancer stem cells, metabolism, and therapeutic significance. Tumor Biol. 2016;37(5):5735–42.
5. Chen W, Dong J, Haiech J, Kilhoffer MC, Zeniou M. Cancer stem cell quiescence and plasticity as major challenges in cancer therapy. Stem Cells Int. 2016;2016.
6. Sahlberg SH, Spiegelberg D, Glimelius B, Stenerlöw B, Nestor M. Evaluation of cancer stem cell markers CD133, CD44, CD24: association with AKT isoforms and radiation resistance in colon cancer cells. PLoS One. 2014;9(4):e94621.
7. Wang J, Wakeman TP, Lathia JD, Hjelmeland AB, Wang X-F, White RR, et al. Notch promotes radioresistance of glioma stem cells. Stem Cells. 2010;28(1):17–28.
8. Hemmati HD, Nakano I, Lazareff JA, Masterman-Smith M, Geschwind DH, Bronner-Fraser M, et al. Cancerous stem cells can arise from pediatric brain tumors. Proc Natl Acad Sci. 2003;100(25):15178–83.
9. Quayle LA, Ottewell PD, Holen I. Chemotherapy resistance and stemness in mitotically quiescent human breast cancer cells identified by fluorescent dye retention. Clin Exp Metastasis. 2018;35(8):831–46.
10. Lobo NA, Shimono Y, Qian D, Clarke MF. The biology of cancer stem cells. Annu Rev Cell Dev Biol. 2007;23:675–99.
11. Mukherjee S, Manna A, Bhattacharjee P, Mazumdar M, Saha S, Chakraborty S, et al. Non-migratory tumorigenic intrinsic cancer stem cells ensure breast cancer metastasis by generation of CXCR4+ migrating cancer stem cells. Oncogene. 2016;35(37):4937–48.
12. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP–dependent transporters. Nat Rev cancer. 2002;2(1):48–58.
13. Diehn M, Cho RW, Lobo NA, Kalisky T, Dorie MJ, Kulp AN, et al. Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature. 2009;458(7239):780–3.

14. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, et al. Identification and expansion of human colon-cancer-initiating cells. Nature. 2007;445(7123):111–5.
15. Baumann M, Krause M, Hill R. Exploring the role of cancer stem cells in radioresistance. Nat Rev Cancer. 2008;8(7):545–54.
16. Sancho P, Burgos-Ramos E, Tavera A, Kheir TB, Jagust P, Schoenhals M, et al. MYC/PGC-1α balance determines the metabolic phenotype and plasticity of pancreatic cancer stem cells. Cell Metab. 2015;22(4):590–605.
17. Wang D, Plukker JTM, Coppes RP. Cancer stem cells with increased metastatic potential as a therapeutic target for esophageal cancer. In: Seminars in cancer biology. Elsevier; 2017. p. 60–6.
18. Iyer AK, Singh A, Ganta S, Amiji MM. Role of integrated cancer nanomedicine in overcoming drug resistance. Adv Drug Deliv Rev. 2013;65(13–14):1784–802.
19. Zhou W, Kallifatidis G, Baumann B, Rausch V, Mattern J, Gladkich J, et al. Dietary polyphenol quercetin targets pancreatic cancer stem cells. Int J Oncol. 2010;37(3):551–61.
20. Mani SA, Guo W, Liao M-J, Eaton EN, Ayyanan A, Zhou AY, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 2008;133(4):704–15.
21. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci. 2003;100(7):3983–8.
22. Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, et al. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell. 2007;1(3):313–23.
23. Collins AT, Berry PA, Hyde C, Stower MJ, Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res. 2005 Dec;65(23):10946–51.
24. Cojoc M, Mäbert K, Muders MH, Dubrovska A. A role for cancer stem cells in therapy resistance: cellular and molecular mechanisms. In: Seminars in cancer biology. Elsevier; 2015. p. 16–27.
25. Yeh D-W, Huang L-R, Chen Y-W, Huang C-YF, Chuang T-H. Interplay between inflammation and stemness in cancer cells: the role of toll-like receptor signaling. J Immunol Res. 2016;2016.
26. Dhawan A, Madani Tonekaboni SA, Taube JH, Hu S, Sphyris N, Mani SA, et al. Mathematical modelling of phenotypic plasticity and conversion to a stem-cell state under hypoxia. Sci Rep. 2016;6(1):1–10.
27. Chen X, Lingala S, Khoobyari S, Nolta J, Zern MA, Wu J. Epithelial mesenchymal transition and hedgehog signaling activation are associated with chemoresistance and invasion of hepatoma subpopulations. J Hepatol. 2011;55(4):838–45.
28. Lytle NK, Ferguson LP, Rajbhandari N, Gilroy K, Fox RG, Deshpande A, et al. A Multiscale Map of the Stem Cell State in Pancreatic Adenocarcinoma. Cell. 2019 Apr;177(3):572-586.e22.
29. Asadzadeh Z, Mansoori B, Mohammadi A, Aghajani M, Haji-Asgarzadeh K, Safarzadeh E, et al. microRNAs in cancer stem cells: Biology, pathways, and therapeutic opportunities. J Cell Physiol. 2019 Jul;234(7):10002–17.
30. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281–97.
31. Pillai RS, Artus CG, Filipowicz W. Tethering of human Ago proteins to mRNA mimics the miRNA-mediated repression of protein synthesis. Rna. 2004;10(10):1518–25.
32. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science (80-). 2007;318(5858):1931–4.
33. Tüfekci KU, Meuwissen RLJ, Genç Ş. The role of microRNAs in biological processes. miRNomics microRNA Biol Comput Anal. 2014;15–31.
34. He B, Zhao Z, Cai Q, Zhang Y, Zhang P, Shi S, et al. miRNA-based biomarkers, therapies, and resistance in Cancer. Int J Biol Sci. 2020;16(14):2628.
35. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell. 2013;152(6):1298–307.
36. Sanchez Calle A, Kawamura Y, Yamamoto Y, Takeshita F, Ochiya T. Emerging roles of long non-coding RNA in cancer. Cancer Sci. 2018 Jul;109(7):2093–100.
37. Andorfer CA, Necela BM, Thompson EA, Perez EA. MicroRNA signatures: clinical biomarkers for the diagnosis and treatment of breast cancer. Trends Mol Med. 2011;17(6):313–9.
38. Jiang L, Lv X, Li J, Li J, Li X, Li W, et al. The status of microRNA-21 expression and its clinical significance in human cutaneous malignant melanoma. Acta Histochem. 2012;114(6):582–8.
39. Takahashi R, Miyazaki H, Ochiya T. The role of microRNAs in the regulation of cancer stem cells. Front Genet. 2014;4:295.
40. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. Nature [Internet]. 2014;505(7483):344–52. Available from: https://doi.org/10.1038/nature12986
41. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011;146(3):353–8.
42. Abdollahzadeh R, Daraei A, Mansoori Y, Sepahvand M, Amoli MM, Tavakkoly-Bazzaz J. Competing endogenous RNA (ceRNA) cross talk and language in ceRNA regulatory networks: a new look at hallmarks of breast cancer. J Cell Physiol. 2019;234(7):10080–100.
43. Cesana M, Cacchiarelli D, Legnini I, Santini T, Sthandier O, Chinappi M, et al. A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell. 2011;147(2):358–69.
44. Li H-Y, Liang J-L, Kuo Y-L, Lee H-H, Calkins MJ, Chang H-T, et al. miR-105/93-3p promotes chemoresistance and circulating miR-105/93-3p acts as a diagnostic biomarker for triple negative breast cancer. Breast Cancer Res. 2017;19(1):1–14.
45. Wang Y, Hou J, He D, Sun M, Zhang P, Yu Y, et al. The emerging function and mechanism of ceRNAs in cancer. Trends Genet. 2016;32(4):211–24.

46. Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, et al. Landscape of transcription in human cells. Nature [Internet]. 2012;489(7414):101–8. Available from: https://doi.org/10.1038/nature11233
47. Nagano T, Mitchell JA, Sanz LA, Pauler FM, Ferguson-Smith AC, Feil R, et al. The Air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin. Science. 2008 Dec;322(5908):1717–20.
48. Guttman M, Donaghey J, Carey BW, Garber M, Grenier JK, Munson G, et al. lincRNAs act in the circuitry controlling pluripotency and differentiation. Nature. 2011 Aug;477(7364):295–300.
49. Dastsooz H, Alizadeh A, Habibzadeh P, Nariman A, Hosseini A, Mansoori Y, et al. LncRNA-miRNA-mRNA Networks of Gastrointestinal Cancers Representing Common and Specific LncRNAs and mRNAs. Front Genet. 2021;12:791919.
50. Ma L, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. RNA Biol [Internet]. 2013/04/15. 2013 Jun;10(6):925–33. Available from: https://pubmed.ncbi.nlm.nih.gov/23696037
51. Loewer S, Cabili MN, Guttman M, Loh Y-H, Thomas K, Park IH, et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. Nat Genet. 2010;42(12):1113–7.
52. Barsyte-Lovejoy D, Lau SK, Boutros PC, Khosravi F, Jurisica I, Andrulis IL, et al. The c-Myc oncogene directly induces the H19 noncoding RNA by allele-specific binding to potentiate tumorigenesis. Cancer Res. 2006;66(10):5330–7.
53. Hou P, Zhao Y, Li Z, Yao R, Ma M, Gao Y, et al. LincRNA-ROR induces epithelial-to-mesenchymal transition and contributes to breast cancer tumorigenesis and metastasis. Cell Death Dis. 2014 Jun;5(6):e1287.
54. Takahashi K, Yan IK, Kogure T, Haga H, Patel T. Extracellular vesicle-mediated transfer of long non-coding RNA ROR modulates chemosensitivity in human hepatocellular cancer. FEBS Open Bio. 2014;4:458–67.
55. Fu Z, Li G, Li Z, Wang Y, Zhao Y, Zheng S, et al. Endogenous miRNA Sponge LincRNA-ROR promotes proliferation, invasion and stem cell-like phenotype of pancreatic cancer cells. Cell death Discov. 2017;3(1):1–10.
56. Cheng E, Lin H. Repressing the repressor: a lincRNA as a MicroRNA sponge in embryonic stem cell self-renewal. Dev Cell. 2013 Apr;25(1):1–2.
57. Yoshino H, Enokida H, Itesako T, Kojima S, Kinoshita T, Tatarano S, et al. Tumor-suppressive micro RNA-143/145 cluster targets hexokinase-2 in renal cell carcinoma. Cancer Sci. 2013;104(12):1567–74.
58. Iio A, Takagi T, Miki K, Naoe T, Nakayama A, Akao Y. DDX6 post-transcriptionally down-regulates miR-143/145 expression through host gene NCR143/145 in cancer cells. Biochim Biophys Acta (BBA)-Gene Regul Mech. 2013;1829(10):1102–10.
59. Kojima S, Enokida H, Yoshino H, Itesako T, Chiyomaru T, Kinoshita T, et al. The tumor-suppressive microRNA-143/145 cluster inhibits cell migration and invasion by targeting GOLM1 in prostate cancer. J Hum Genet. 2014;59(2):78–87.
60. Gunaratne PH. Embryonic stem cell microRNAs: defining factors in induced pluripotent (iPS) and cancer (CSC) stem cells? Curr Stem Cell Res Ther. 2009;4(3):168–77.
61. Herreros-Villanueva M, Bujanda L, Billadeau DD, Zhang J-S. Embryonic stem cell factors and pancreatic cancer. World J Gastroenterol WJG. 2014;20(9):2247.
62. Wang Y, Xu Z, Jiang J, Xu C, Kang J, Xiao L, et al. Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal. Dev Cell. 2013 Apr;25(1):69–80.
63. Zhou X, Gao Q, Wang J, Zhang X, Liu K, Duan Z. Linc-RNA-RoR acts as a "sponge" against mediation of the differentiation of endometrial cancer stem cells by microRNA-145. Gynecol Oncol. 2014;133(2):333–9.
64. Liu T, Chi H, Chen J, Chen C, Huang Y, Xi H, et al. Curcumin suppresses proliferation and in vitro invasion of human prostate cancer stem cells by ceRNA effect of miR-145 and lncRNA-ROR. Gene. 2017 Oct;631:29–38.
65. Kumar SM, Liu S, Lu H, Zhang H, Zhang PJ, Gimotty PA, et al. Acquired cancer stem cell phenotypes through Oct4-mediated dedifferentiation. Oncogene. 2012;31(47):4898–911.
66. Reers S, Pfannerstill A-C, Maushagen R, Pries R, Wollenberg B. Stem cell profiling in head and neck cancer reveals an Oct-4 expressing subpopulation with properties of chemoresistance. Oral Oncol. 2014;50(3):155–62.
67. Chen Y-C, Hsu H-S, Chen Y-W, Tsai T-H, How C-K, Wang C-Y, et al. Oct-4 expression maintained cancer stem-like properties in lung cancer-derived CD133-positive cells. PLoS One. 2008;3(7):e2637.
68. Yan ZY, Sun XC. LincRNA-ROR functions as a ceRNA to regulate Oct4, Sox2, and Nanog expression by sponging miR-145 and its effect on biologic characteristics of colonic cancer stem cells. Zhonghua Bing li xue za zhi= Chinese J Pathol. 2018;47(4):284–90.
69. Takeda J, Seino S, Bell GI. Human Oct3 gene family: cDNA sequences, alternative splicing, gene organization, chromosomal location, and expression at low levels in adult tissues. Nucleic Acids Res. 1992;20(17):4613–20.
70. Cantz T, Key G, Bleidiβel M, Gentile L, Han DW, Brenne A, et al. Absence of OCT4 expression in somatic tumor cell lines. Stem Cells. 2008;26(3):692–7.
71. Li D, Yang Z-K, Bu J-Y, Xu C-Y, Sun H, Tang J-B, et al. OCT4B modulates OCT4A expression as ceRNA in tumor cells. Oncol Rep. 2015;33(5):2622–30.
72. Maugeri-Saccà M, De Maria R. Hippo pathway and breast cancer stem cells. Crit Rev Oncol Hematol. 2016;99:115–22.
73. Shibata M, Ham K, Hoque MO. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. Int J cancer. 2018;143(9):2133–44.
74. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the roots of cancer. Cancer Cell. 2016;29(6):783–803.
75. Lu T, Li Z, Yang Y, Ji W, Yu Y, Niu X, et al. The Hippo/YAP1 pathway interacts with FGFR1 signaling to maintain stemness in lung cancer. Cancer Lett. 2018;423:36–46.
76. Bora-Singhal N, Nguyen J, Schaal C, Perumal D, Singh S, Coppola D, et al. YAP1 regulates OCT4 activity and SOX2 expression to facilitate self-renewal and vascular mimicry of stem-like cells. Stem Cells. 2015;33(6):1705–18.

77. Strnadel J, Choi S, Fujimura K, Wang H, Zhang W, Wyse M, et al. eIF5A-PEAK1 Signaling Regulates YAP1/TAZ Protein Expression and Pancreatic Cancer Cell GrowtheIF5A/PEAK1/YAP1 Controls Pancreatic Cancer Cell Growth. Cancer Res. 2017;77(8):1997–2007.
78. Tremblay AM, Camargo FD. Hippo signaling in mammalian stem cells. In: Seminars in cell & developmental biology. Elsevier; 2012. p. 818–26.
79. Kim J, Jo H, Hong H, Kim MH, Kim JM, Lee J-K, et al. Actin remodelling factors control ciliogenesis by regulating YAP/TAZ activity and vesicle trafficking. Nat Commun. 2015;6(1):1–13.
80. Moroishi T, Hayashi T, Pan W-W, Fujita Y, Holt M V, Qin J, et al. The Hippo pathway kinases LATS1/2 suppress cancer immunity. Cell. 2016;167(6):1525–39.
81. Hansen CG, Moroishi T, Guan K-L. YAP and TAZ: a nexus for Hippo signaling and beyond. Trends Cell Biol. 2015;25(9):499–513.
82. Zheng L, Xiang C, Li X, Guo Q, Gao L, Ni H, et al. STARD13-correlated ceRNA network-directed inhibition on YAP/TAZ activity suppresses stemness of breast cancer via co-regulating Hippo and Rho-GTPase/F-actin signaling. J Hematol Oncol. 2018;11(1):1–18.
83. Ohgushi M, Minaguchi M, Sasai Y. Rho-signaling-directed YAP/TAZ activity underlies the long-term survival and expansion of human embryonic stem cells. Cell Stem Cell. 2015;17(4):448–61.
84. Nagaraja GM, Kandpal RP. Chromosome 13q12 encoded Rho GTPase activating protein suppresses growth of breast carcinoma cells, and yeast two-hybrid screen shows its interaction with several proteins. Biochem Biophys Res Commun. 2004;313(3):654–65.
85. Tang F, Zhang R, He Y, Zou M, Guo L, Xi T. MicroRNA-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells. PLoS One. 2012;7(5):e35435.
86. Wang Z, Wu Y, Wang H, Zhang Y, Mei L, Fang X, et al. Interplay of mevalonate and Hippo pathways regulates RHAMM transcription via YAP to modulate breast cancer cell motility. Proc Natl Acad Sci. 2014;111(1):E89–98.
87. Zhao L, Lou G, Li A, Liu Y. lncRNA MALAT1 modulates cancer stem cell properties of liver cancer cells by regulating YAP1 expression via miR-375 sponging. Mol Med Rep. 2020;22(2):1449–57.
88. Zhang X, Hamblin MH, Yin K-J. The long noncoding RNA Malat1: Its physiological and pathophysiological functions. RNA Biol. 2017 Dec;14(12):1705–14.
89. Liu D, Zhu Y, Pang J, Weng X, Feng X, Guo Y. Retracted: Knockdown of long non-coding RNA MALAT1 inhibits growth and motility of human hepatoma cells via modulation of miR-195. Wiley Online Library; 2018.
90. Yuan P, Cao W, Zang Q, Li G, Guo X, Fan J. The HIF-2α-MALAT1-miR-216b axis regulates multi-drug resistance of hepatocellular carcinoma cells via modulating autophagy. Biochem Biophys Res Commun. 2016;478(3):1067–73.
91. Yoshimoto R, Mayeda A, Yoshida M, Nakagawa S. MALAT1 long non-coding RNA in cancer. Biochim Biophys Acta. 2016 Jan;1859(1):192–9.
92. Jiao F, Hu H, Han T, Yuan C, Wang L, Jin Z, et al. Long noncoding RNA MALAT-1 enhances stem cell-like phenotypes in pancreatic cancer cells. Int J Mol Sci. 2015 Mar;16(4):6677–93.
93. Han Y, Zhou L, Wu T, Huang Y, Cheng Z, Li X, et al. Downregulation of lncRNA-MALAT1 affects proliferation and the expression of stemness markers in glioma stem cell line SHG139S. Cell Mol Neurobiol. 2016;36(7):1097–107.
94. Chen Y, Huang W, Sun W, Zheng B, Wang C, Luo Z, et al. LncRNA MALAT1 Promotes Cancer Metastasis in Osteosarcoma via Activation of the PI3K-Akt Signaling Pathway. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 2018;51(3):1313–26.
95. Li X. MiR-375, a microRNA related to diabetes. Gene. 2014;533(1):1–4.
96. Yan J, Lin J, He X. The emerging role of miR-375 in cancer. Int J cancer. 2014;135(5):1011–8.
97. Zhou N, Wu J, Wang X, Sun Z, Han Q, Zhao L. Low-level expression of microRNA-375 predicts poor prognosis in hepatocellular carcinoma. Tumor Biol. 2016;37(2):2145–52.
98. Cao S, Wang G, Wang J, Li C, Zhang L. Hsa_circ_101280 promotes hepatocellular carcinoma by regulating miR-375/JAK2. Immunol Cell Biol. 2019;97(2):218–28.
99. Li L, Jia L, Ding Y. Upregulation of miR-375 inhibits human liver cancer cell growth by modulating cell proliferation and apoptosis via targeting ErbB2. Oncol Lett. 2018;16(3):3319–26.
100. He XX, Chang Y, Meng FY, Wang MY, Xie QH, Tang F, et al. MicroRNA-375 targets AEG-1 in hepatocellular carcinoma and suppresses liver cancer cell growth in vitro and in vivo. Oncogene. 2012;31(28):3357–69.
101. Chang Y, Yan W, He X, Zhang L, Li C, Huang H, et al. miR-375 inhibits autophagy and reduces viability of hepatocellular carcinoma cells under hypoxic conditions. Gastroenterology. 2012;143(1):177–87.
102. Misra S, Hascall VC, Markwald RR, Ghatak S. Interactions between hyaluronan and its receptors (CD44, RHAMM) regulate the activities of inflammation and cancer. Front Immunol. 2015;6:201.
103. Yan Y, Zuo X, Wei D. Concise review: emerging role of CD44 in cancer stem cells: a promising biomarker and therapeutic target. Stem Cells Transl Med. 2015;4(9):1033–43.
104. Rane JK, Scaravilli M, Ylipää A, Pellacani D, Mann VM, Simms MS, et al. MicroRNA expression profile of primary prostate cancer stem cells as a source of biomarkers and therapeutic targets. Vol. 67, European urology. Switzerland; 2015. p. 7–10.
105. Oktem G, Bilir A, Uslu R, Inan V. S, Demiray B. S, Atmaca H, et al. Expression profiling of stem cell signaling alters with spheroid formation in CD133high/CD44high prostate cancer stem cells. Oncol Lett [Internet]. 2014;7(6):2103–9. Available from: https://doi.org/10.3892/ol.2014.1992

106. Jeyapalan Z, Deng Z, Shatseva T, Fang L, He C, Yang BB. Expression of CD44 3′-untranslated region regulates endogenous microRNA functions in tumorigenesis and angiogenesis. Nucleic Acids Res. 2011;39(8):3026–41.
107. Schwinn N, Vokhminova D, Sucker A, Textor S, Striegel S, Moll I, et al. Interferon-γ down-regulates NKG2D ligand expression and impairs the NKG2D-mediated cytolysis of MHC class I-deficient melanoma by natural killer cells. Int J cancer. 2009;124(7):1594–604.
108. Li W (Jess), Wang Y, Liu R, Kasinski AL, Shen H, Slack FJ, et al. MicroRNA-34a: Potent Tumor Suppressor, Cancer Stem Cell Inhibitor, and Potential Anticancer Therapeutic [Internet]. Vol. 9, Frontiers in Cell and Developmental Biology . 2021. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2021.640587
109. Liu C, Kelnar K, Liu B, Chen X, Calhoun-Davis T, Li H, et al. The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. Nat Med. 2011;17(2):211–5.
110. Heinemann A, Zhao F, Pechlivanis S, Eberle J, Steinle A, Diederichs S, et al. Tumor Suppressive MicroRNAs miR-34a/c Control Cancer Cell Expression of ULBP2, a Stress-Induced Ligand of the Natural Killer Cell Receptor NKG2DNKG2D Ligand Regulation. Cancer Res. 2012;72(2):460–71.
111. Weng J, Han X, Liu K, Yang J, Wei S, Zhang Y, et al. CD44 3′-untranslated region functions as a competing endogenous RNA to enhance NK sensitivity of liver cancer stem cell by regulating ULBP2 expression. Int J Biol Sci. 2019;15(8):1664.
112. Hsieh I-S, Chang K-C, Tsai Y-T, Ke J-Y, Lu P-J, Lee K-H, et al. MicroRNA-320 suppresses the stem cell-like characteristics of prostate cancer cells by downregulating the Wnt/beta-catenin signaling pathway. Carcinogenesis. 2013;34(3):530–8.
113. Tamura M, Uyama M, Sugiyama Y, Sato M. Canonical Wnt signaling activates miR-34 expression during osteoblastic differentiation. Mol Med Rep. 2013;8(6):1807–11.
114. Bräutigam C, Raggioli A, Winter J. The Wnt/β-catenin pathway regulates the expression of the miR-302 cluster in mouse ESCs and P19 cells. PLoS One. 2013;8(9):e75315.
115. Cai W-Y, Wei T-Z, Luo Q-C, Wu Q-W, Liu Q-F, Yang M, et al. The Wnt–β-catenin pathway represses let-7 microRNA expression through transactivation of Lin28 to augment breast cancer stem cell expansion. J Cell Sci. 2013;126(13):2877–89.
116. Li S, Zhou J, Wang Z, Wang P, Gao X, Wang Y. Long noncoding RNA GAS5 suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p. Biomed Pharmacother. 2018 Aug;104:451–7.
117. Zhao X, Liu Y, Zheng J, Liu X, Chen J, Liu L, et al. GAS5 suppresses malignancy of human glioma stem cells via a miR-196a-5p/FOXO1 feedback loop. Biochim Biophys Acta (BBA)-Molecular Cell Res. 2017;1864(10):1605–17.
118. Yan Q, Tian Y, Hao F. Downregulation of lncRNA UCA1 inhibits proliferation and invasion of cervical cancer cells through miR-206 expression. Oncol Res Featur Preclin Clin Cancer Ther. 2021;
119. Sun Y, Jin J-G, Mi W-Y, Zhang S-R, Meng Q, Zhang S-T. Long noncoding RNA UCA1 targets miR-122 to promote proliferation, migration, and invasion of glioma cells. Oncol Res. 2018;26(1):103.
120. He Z, Wang Y, Huang G, Wang Q, Zhao D, Chen L. The lncRNA UCA1 interacts with miR-182 to modulate glioma proliferation and migration by targeting iASPP. Arch Biochem Biophys. 2017 Jun;623–624:1–8.
121. Liang C, Yang Y, Guan J, Lv T, Qu S, Fu Q, et al. LncRNA UCA1 sponges miR-204-5p to promote migration, invasion and epithelial-mesenchymal transition of glioma cells via upregulation of ZEB1. Pathol Res Pract. 2018 Sep;214(9):1474–81.
122. He Z, You C, Zhao D. Long non-coding RNA UCA1/miR-182/PFKFB2 axis modulates glioblastoma-associated stromal cells-mediated glycolysis and invasion of glioma cells. Biochem Biophys Res Commun. 2018;500(3):569–76.
123. Eser PÖ, Jänne PA. TGFβ pathway inhibition in the treatment of non-small cell lung cancer. Pharmacol Ther. 2018;184:112–30.
124. Kali A, Ostapchuk YO, Belyaev NN. TNFα and TGFβ-1 synergistically increase the cancer stem cell properties of MiaPaCa-2 cells. Oncol Lett. 2017;14(4):4647–58.
125. Li Z, Liu H, Zhong Q, Wu J, Tang Z. LncRNA UCA1 is necessary for TGF-β-induced epithelial–mesenchymal transition and stemness via acting as a ceRNA for Slug in glioma cells. FEBS Open Bio [Internet]. 2018 Nov 1;8(11):1855–65. Available from: https://doi.org/10.1002/2211-5463.12533
126. Deng B, Wang B, Fang J, Zhu X, Cao Z, Lin Q, et al. MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2. Sci Rep. 2016;6(1):1–11.
127. Xu M, Gu M, Zhang K, Zhou J, Wang Z, Da J. miR-203 inhibition of renal cancer cell proliferation, migration and invasion by targeting of FGF2. Diagn Pathol. 2015;10(1):1–9.
128. Chi Y, Jin Q, Liu X, Xu L, He X, Shen Y, et al. miR-203 inhibits cell proliferation, invasion, and migration of non-small-cell lung cancer by downregulating RGS 17. Cancer Sci. 2017;108(12):2366–72.
129. Takeshita N, Mori M, Kano M, Hoshino I, Akutsu Y, Hanari N, et al. miR-203 inhibits the migration and invasion of esophageal squamous cell carcinoma by regulating LASP1. Int J Oncol. 2012;41(5):1653–61.
130. Obayashi M, Yoshida M, Tsunematsu T, Ogawa I, Sasahira T, Kuniyasu H, et al. microRNA-203 suppresses invasion and epithelial-mesenchymal transition induction via targeting NUAK1 in head and neck cancer. Oncotarget. 2016;7(7):8223.
131. Miao Z, Guo X, Tian L. The long noncoding RNA NORAD promotes the growth of gastric cancer cells by sponging miR-608. Gene. 2019;687:116–24.
132. Tao W, Li Y, Zhu M, Li C, Li P. LncRNA NORAD promotes proliferation and inhibits apoptosis of gastric cancer by regulating miR-214/Akt/mTOR axis. Onco Targets Ther. 2019;12:8841.
133. Lei Y, Wang YH, Wang XF, Bai J. LINC00657 promotes the development of colon cancer by activating PI3K/AKT pathway. Eur Rev Med Pharmacol Sci. 2018;22(19):6315–23.

134. Zhao L, Liu C, Yan S, Hu G, Xiang K, Xiang H, et al. LINC00657 promotes colorectal cancer stem-like cell invasion by functioning as a miR-203a sponge. Biochem Biophys Res Commun [Internet]. 2020;529(2):500–6. Available from: https://www.sciencedirect.com/science/article/pii/S0006291X20307750
135. Raveh E, Matouk IJ, Gilon M, Hochberg A. The H19 Long non-coding RNA in cancer initiation, progression and metastasis - a proposed unifying theory. Mol Cancer. 2015 Nov;14:184.
136. Jiang X, Yan Y, Hu M, Chen X, Wang Y, Dai Y, et al. Increased level of H19 long noncoding RNA promotes invasion, angiogenesis, and stemness of glioblastoma cells. J Neurosurg. 2016;124(1):129–36.
137. Yang F, Bi J, Xue X, Zheng L, Zhi K, Hua J, et al. Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. FEBS J. 2012;279(17):3159–65.
138. Poirier F, Chan CT, Timmons PM, Robertson EJ, Evans MJ, Rigby PW. The murine H19 gene is activated during embryonic stem cell differentiation in vitro and at the time of implantation in the developing embryo. Development. 1991;113(4):1105–14.
139. Bauderlique-Le Roy H, Vennin C, Brocqueville G, Spruyt N, Adriaenssens E, Bourette RP. Enrichment of human stem-like prostate cells with s-SHIP promoter activity uncovers a role in stemness for the long noncoding RNA H19. Stem Cells Dev. 2015;24(10):1252–62.
140. Ma C, Nong K, Zhu H, Wang W, Huang X, Yuan Z, et al. H19 promotes pancreatic cancer metastasis by derepressing let-7's suppression on its target HMGA2-mediated EMT. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2014 Sep;35(9):9163–9.
141. Peng F, Li T-T, Wang K-L, Xiao G-Q, Wang J-H, Zhao H-D, et al. H19/let-7/LIN28 reciprocal negative regulatory circuit promotes breast cancer stem cell maintenance. Cell Death Dis. 2018;8(1):e2569–e2569.
142. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science (80-). 2007;318(5858):1917–20.
143. Bazley FA, Liu CF, Yuan X, Hao H, All AH, De Los Angeles A, et al. Direct reprogramming of human primordial germ cells into induced pluripotent stem cells: efficient generation of genetically engineered germ cells. Stem Cells Dev. 2015;24(22):2634–48.
144. King CE, Cuatrecasas M, Castells A, Sepulveda AR, Lee J-S, Rustgi AK. LIN28B promotes colon cancer progression and metastasis. Cancer Res. 2011;71(12):4260–8.
145. Viswanathan SR, Daley GQ. Lin28: A microRNA regulator with a macro role. Cell. 2010;140(4):445–9.
146. Heo I, Joo C, Cho J, Ha M, Han J, Kim VN. Lin28 mediates the terminal uridylation of let-7 precursor MicroRNA. Mol Cell. 2008;32(2):276–84.
147. Zhou J, Ng S-B, Chng W-J. LIN28/LIN28B: an emerging oncogenic driver in cancer stem cells. Int J Biochem Cell Biol. 2013 May;45(5):973–8.
148. Büssing I, Slack FJ, Großhans H. let-7 microRNAs in development, stem cells and cancer. Trends Mol Med. 2008;14(9):400–9.
149. Huang Y, Wang L, Liu D. HOTAIR regulates colorectal cancer stem cell properties and promotes tumorigenicity by sponging miR-211-5p and modulating FLT-1. Cell Cycle. 2021;20(19):1999–2009.
150. Zhang S, Ji W-W, Wei W, Zhan L-X, Huang X. Long noncoding RNA Meg3 sponges miR-708 to inhibit intestinal tumorigenesis via SOCS3-repressed cancer stem cells growth. Cell Death Dis. 2021;13(1):1–13.
151. Zhao Y, Zhu Z, Shi S, Wang J, Li N. Long non-coding RNA MEG3 regulates migration and invasion of lung cancer stem cells via miR-650/SLC34A2 axis. Biomed Pharmacother. 2019 Dec;120:109457.
152. Cheng FHC, Lin H, Hwang T, Chen Y, Huang R, Chang C, et al. E2F6 functions as a competing endogenous RNA, and transcriptional repressor, to promote ovarian cancer stemness. Cancer Sci. 2019;110(3):1085–95.
153. Han P, Yang H, Li X, Wu J, Wang P, Liu D, et al. Identification of a novel cancer stemness-associated ceRNA axis in lung adenocarcinoma via stemness indices analysis. Oncol Res Featur Preclin Clin Cancer Ther. 2021;28(7–8):715–29.
154. Wulf-Johansson H, Lock Johansson S, Schlosser A, Trommelholt Holm A, Melholt Rasmussen L, Mickley H, et al. Localization of microfibrillar-associated protein 4 (MFAP4) in human tissues: clinical evaluation of serum MFAP4 and its association with various cardiovascular conditions. PLoS One. 2013;8(12):e82243.
155. Yang J, Song H, Chen L, Cao K, Zhang Y, Li Y, et al. Integrated analysis of microfibrillar-associated proteins reveals MFAP4 as a novel biomarker in human cancers. Epigenomics. 2019;11(1):5–21.
156. Davalieva K, Kostovska IM, Kiprijanovska S, Markoska K, Kubelka-Sabit K, Filipovski V, et al. Proteomics analysis of malignant and benign prostate tissue by 2D DIGE/MS reveals new insights into proteins involved in prostate cancer. Prostate. 2015;75(14):1586–600.
157. Zaravinos A, Lambrou GI, Boulalas I, Delakas D, Spandidos DA. Identification of common differentially expressed genes in urinary bladder cancer. PLoS One. 2011;6(4):e18135.
158. Feng Y-Y, Liu C-H, Xue Y, Chen Y-Y, Wang Y-L, Wu X-Z. MicroRNA-147b promotes lung adenocarcinoma cell aggressiveness through negatively regulating microfibril-associated glycoprotein 4 (MFAP4) and affects prognosis of lung adenocarcinoma patients. Gene. 2020;730:144316.
159. Salavaty A, Rezvani Z, Najafi A. Survival analysis and functional annotation of long non-coding RNAs in lung adenocarcinoma. J Cell Mol Med. 2019;23(8):5600–17.
160. Zhao Z, Zhang C, Li M, Yu X, Liu H, Chen Q, et al. Integrative analysis of miRNA-mediated competing endogenous RNA network reveals the lncRNAs-mRNAs interaction in glioblastoma stem cell differentiation. Curr Bioinform. 2020;15(10):1187–96.