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The Impact of Non-coding RNAs in the Epithelial to Mesenchymal Transition

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Epithelial to mesenchymal transition (EMT) is a course of action that enables a polarized epithelial cell to undertake numerous biochemical alterations that allow it to adopt features of mesenchymal cells such as high migratory ability, invasive properties, resistance to apoptosis, and importantly higher-order formation of extracellular matrix elements. EMT has important roles in implantation and gastrulation of the embryo, inflammatory reactions and fibrosis, and transformation of cancer cells, their invasiveness and metastatic ability. Regarding the importance of EMT in the invasive progression of cancer, this process has been well studies in in this context. Non-coding RNAs (ncRNAs) have been shown to exert critical function in the regulation of cellular processes that are involved in the EMT. These processes include regulation of some transcription factors namely SNAI1 and SNAI2, ZEB1 and ZEB2, Twist, and E12/E47, modulation of chromatin configuration, alternative splicing, and protein stability and subcellular location of proteins. In the present paper, we describe the influence of ncRNAs including microRNAs and long non-coding RNAs in the EMT process and their application as biomarkers for this process and cancer progression and their potential as therapeutic targets.

Keywords: lncRNA, miRNA, epithelial to mesenchymal transition, expression, biomarker

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INTRODUCTION

Epithelial to mesenchymal transition (EMT) is a course of action that permits polarized epithelial cells, that typically interrelate with basement membrane through their basal facet, to undertake numerous biochemical alterations that allow them to adopt features of mesenchymal cells such as high migratory ability, invasive properties, resistance to apoptosis, and importantly the higher-order formation of extracellular matrix elements (Kalluri and Neilson, 2003). The EMT process is completed by the destruction of the basement membranes and development of mesenchymal cells that are able to roam from their original epithelial layer (Roche, 2018). Induction and establishment of the EMT program is associated with activation of several transcription factors

and cell-surface markers, reformation and activation of cytoskeletal proteins, synthesis of ECM-degenerating enzymes, and alteration in the expressions of several non-coding RNAs (ncRNAs) (Kalluri and Neilson, 2003; Roche, 2018). At least three types of EMT are recognized. These distinct types are involved in the processes of implantation and gastrulation of embryos, inflammatory responses and fibrosis, and transformation of cancer cells, their invasiveness and metastatic ability, respectively (Kalluri and Neilson, 2003).

EMT IN PHYSIOLOGICAL PROCESSES

Epithelial to mesenchymal transition has critical roles in generation of various tissues in the course of development of organisms. Importantly, EMT has an indispensable role in the gastrulation of metazoans and delamination of neural crest cells in vertebrate embryos (Thiery et al., 2009). EMT also partakes in wound healing (Kim et al., 2014). In addition, EMT regulates function of embryonic stem cells through various routes (Kim et al., 2014). Conversion of epithelial cells to mesenchymal cells has been detected in the course of differentiation of embryonic stem cells. In humans, differentiation of these cells is achieved through up-regulation of N-cadherin instead of E-cadherin, enhancement of vimentin levels, over-expression of E-cadherin-suppressing molecules including Snail and Slug, and activation of gelatinase and upsurge in motility of cells (Kim et al., 2014).

EMT IN CANCER

In the context of cancer, EMT is activated by several factors such as hypoxia, cytokines, and growth factors. These molecules are produced by numerous cells that are present in the tumor milieu in response to metabolic alteration, innate and adaptive immune reactions, and administration of antitumor drugs (Roche, 2018). EMT is associated with comprehensive changes in the expression profile of genes. This expression switch is accomplished through an integrative regulatory network that consists of a number of transcription factors namely SNAI1 and SNAI2, ZEB1 and ZEB2, Twist, and E12/E47, ncRNAs, and other factors that modulate chromatin configuration, alternative splicing, and protein stability and subcellular location (De Craene and Berx, 2013). The most important feature of EMT is the over-expression of N-cadherin and the subsequent downregulation of E-cadherin (Loh et al., 2019). This process has important implications in the design of anticancer therapeutic agents (Marcucci et al., 2016) and, moreover, has fundamental roles in the metastatic potential of cancer cells, a process whose reversion is critical in cancer treatment (Roche, 2018). Thus, identification of the molecular pathways that control EMT process is a prerequisite for development of novel anticancer therapies. In the current paper, we describe the role of ncRNAs including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in the EMT process and their application as biomarkers for this process and cancer progression and their potential as therapeutic targets.

miRNAs AND EMT

miRNAs are transcripts with sizes around 22 to 24 nucleotides. They are principally bind with the 3′ UTR of selected transcripts to suppress their translation or degrade them via slicer-dependent route (Macfarlane and Murphy, 2010). Several miRNAs influence the EMT process in different cancer types. In lung cancer, miR-451a has a central role in blocking EMT and conferring sensitivity to doxorubicin through this mechanism. miR-451a decreases expressions of N-cadherin and Vimentin, whereas it surges expression of E-cadherin. Functional studies show that the direct interaction between miR-451a and c-Myc contributes in blocking EMT and chemoresistance in lung cancer cells (Tao et al., 2020). The well-known oncogenic miRNA miR-21 has a noticeable role in induction of EMT through modulation of the PTEN/Akt/GSK3 beta pathway and regulation of transcription of E-cadherin, vimentin, snail, slug and β-catenin (Dai L. et al., 2019). In prostate cancer patients, expression of miR-210-3p is increased in bone metastatic specimens compared with non-bone metastatic specimens. Up-regulation of this miRNA is associated with PSA concentrations in serum, Gleason grade and metastatic probability to bone in these patients. *In vitro* experiments show the effect of miR-210-3p in augmentation of EMT, invasion and migration of prostate cancer cells. Notably, animal studies show that miR-210-3p knockdown decreases bone metastasis of PC-3 cells. This miRNA preserves the constant induction of NF-κB signaling through modulating expression of SOCS1 and TNIP1 (Ren et al., 2017). Expression of miR-23a is augmented in metastatic breast cancer cells and in patients with lymph node involvement. Notably, expression of this miRNA is increased after treatment of breast cancer cells with TGF-β1. Importantly, both cell line assays and *in vivo* tests show that miR-23a silencing suppressed TGF-β1-stimulated EMT, migration, invasiveness and metastatic probability. The role of miR-23a in EMT is exerted via its binding with CDH1, a critical gene in EMT process. Remarkably, Wnt/β-catenin signaling is also engaged in miR-23a facilitated progression of EMT (Ma et al., 2017). In colorectal cancer, expression of miR-330 has been down-regulated parallel with up-regulation of HMGA2 levels and poor clinical outcome. Stable up-regulation of miR-330 in these cell lines has decreased HMGA2 levels, enhanced apoptosis and decreased migratory potential and viability of these cells. Notably, this miRNA has also reduced expressions of EMT markers including Snail-1, E-cadherin and VEGF as well as some other oncogenic proteins namely SMAD3 and AKT (Mansoori et al., 2020). In this type of cancer, miR-145-5p, miR-383-5p, miR-3622a-3p, miR-205 and miR-200b inhibit EMT process through targeting CDCA3, SGK1, SALL4, MDM4 and HIF-1α, respectively (Shang et al., 2017; Chong et al., 2019; Chang et al., 2020; Chen et al., 2020; Fan and Wang, 2020).

Figure 1 depicts the impacts of miRNAs in the EMT process in non-small cell lung cancer (NSCLC).

Supplementary Table 1 displays the role of individual miRNAs in the EMT process in diverse human cancers.

As EMT has a central part in the progression of cancer, EMT-associated miRNAs have prominent roles in the determination of patients' survival. For instance, over-expression of miR-200c-3p,

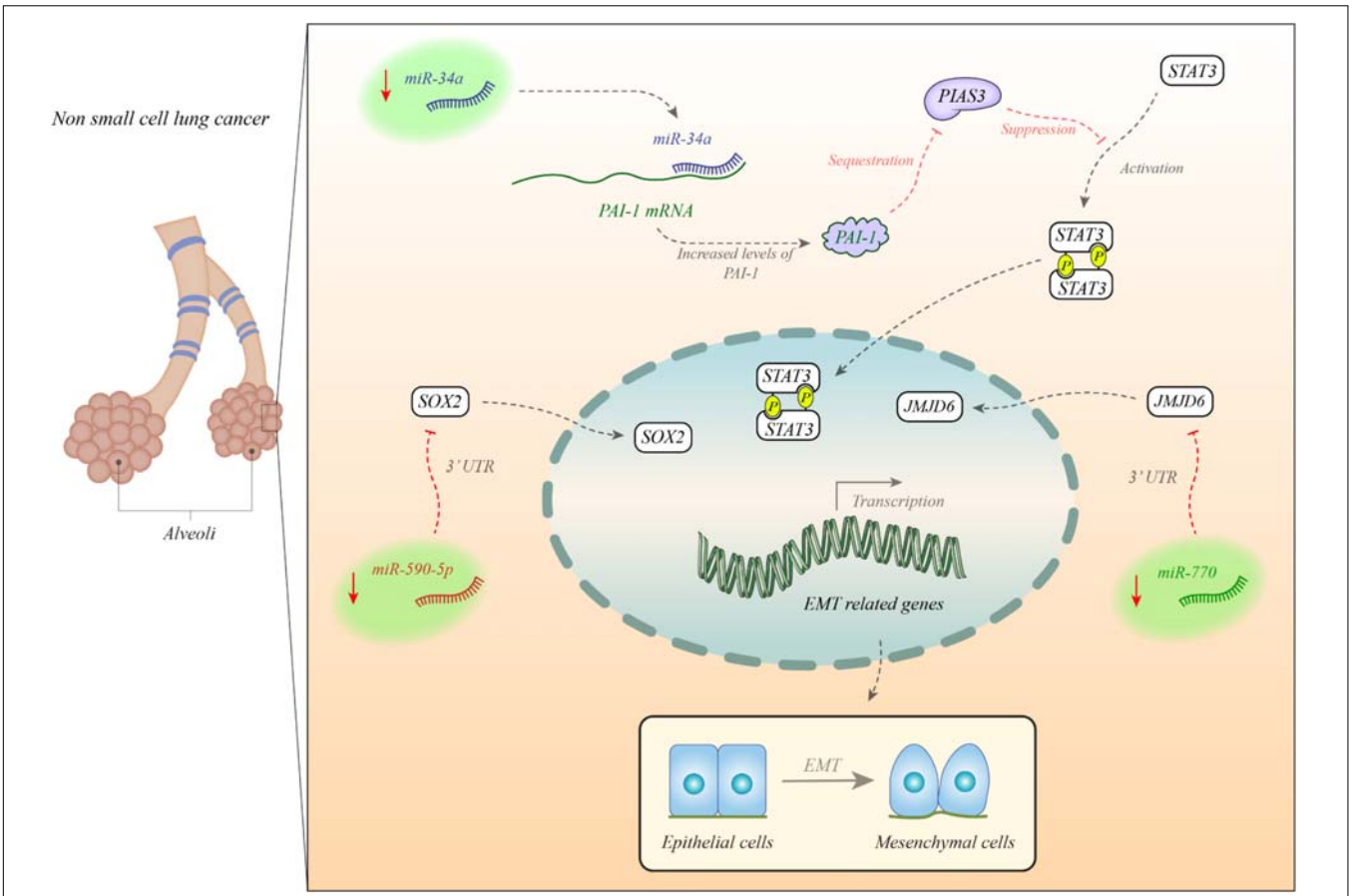

FIGURE 1 | miR-34a is decreased in non-small cell lung cancer (NSCLC). miR-34a blocks expression of PAI. PAI has a role in suppression of PIAS3 expression and blocking its effects on STAT3. STAT3 enhances expression of EMT-related genes (Wang D.X. et al., 2017). In addition, miR-770 and miR-590-5p are decreased in these patients. These miRNA suppress expression of JMJD6 and SOX2, respectively. Under-expression of these miRNAs leads to over-expression of EMT genes.

miR-99a and miR-92b is linked with prolonged survival in lung cancer, ovarian cancer and breast cancer patients (Li Y.Y. et al., 2019; Zhang L. et al., 2019; Wang H.Y. et al., 2020). Conversely, up-regulation of miR-199b-5p and miR-210-3p is linked with poor survival in prostate cancer patients (Ren et al., 2017; Zhao et al., 2019). **Table 1** shows the result of studies that have appraised the prognostic role of EMT-associated miRNAs in diverse cancers.

miRNA ROLES IN EMT IN NON-CANCEROUS CONDITIONS

Expression of miR-29b has been decreased by silica and has affected the mesenchymal-epithelial transition (MET) in RLE-6TN cells. Besides, up-regulation of miR-29b can suppress silica-induced EMT in animals, precluding lung fibrosis, and enhancing respiratory function. Therefore, miR-29b has been suggested as a negative modulator of silicosis fibrosis, possibly through enhancing MET and inhibiting EMT in the lung (Sun et al., 2019). Moreover, miR-200b/c-3p have been shown to modulate epithelial plasticity and suppress skin wound healing through affecting TGF-β-mediated RAC1 signaling (Tang et al., 2020).

LncRNAs AND EMT

LncRNAs are regulatory transcripts with diverse sizes ranging from 200 nucleotides to more than thousands nucleotides. These transcripts regulate expression of genes through altering chromatin configuration, acting as enhances, sponging diverse molecules particularly miRNAs and altering stability of transcripts (Fang and Fullwood, 2016). Through modulation of activity of several cancer-related signaling cascades, lncRNAs modulate metastatic potential of tumor cells (Ghafouri-Fard et al., 2021a,b). Several lncRNAs play a part in the modulation of EMT processes. For instance, expression of NEAT1 is augmented in cervical cancer tissues in correlation with poor survival of patients. This lncRNA directly inhibits expression of miR-361, a miRNA that suppresses HSP90 to impede the invasion and EMT phenotype. Thus, NEAT1 is regarded as a pro-EMT lncRNA in cervical cancer (Xu D. et al., 2020). MALAT1 enhances the EMT features and cisplatin resistance of oral squamous cell

TABLE 1 | Prognostic roles of EMT-associated miRNAs in cancer (ACT: adjacent control tissue).

Sample number	Kaplan-Meier analysis	References
70 pairs of LC and ACTs	High miR-200c-3p expression was linked with longer survival.	Wang H.Y. et al., 2020
179 pairs of LC and ACTs	High expression of miR-616-5p was linked with poor overall survival.	Shi et al., 2017
49 pairs of LC and ACTs	Decreased miR-874 expression was linked with poor prognosis.	Wang S. et al., 2020
47 pairs of OC and ACTs	Decreased miR-99a expression in was linked with poor prognosis.	Zhang L. et al., 2019
51 pairs of BC and ACTs	Decreased miR-92b expression was linked with poor prognosis.	Li Y.Y. et al., 2019
60 pairs of BC and ACTs	Decreased miR−516a−3p expression was linked with poor prognosis.	Chi et al., 2019
117 pairs of BLC and ACTs	Decreased miR-221expression was linked with poor prognosis.	Li F. et al., 2019
300 pairs of CRC and ACTs	Decreased miR−330 expression was linked with poor prognosis.	Mansoori et al., 2020
80 pairs of CRC and ACTs	High expression of miR-3622a-3p was linked with better overall survival.	Chang et al., 2020
4 pairs of CRC and ACTs	Decreased miR−598 expression was linked with poor prognosis.	Wang Y. et al., 2017
93 pairs of BC and ACTs	Higher expression of miR-365-3p was linked with better overall survival.	Gao and Tian, 2020
Breast cancer	Higher expression of miR-335 was linked with poor overall survival.	Chen et al., 2019
30 pairs of CRC and ACTs	Decreased miR-195-5p expression was linked with poor prognosis.	Lin et al., 2019
157 pairs of PaC and ACTs	Decreased miR-3656 expression was linked with poor prognosis.	Yang R.M. et al., 2017
36 OC tissues and 14 normal ovarian tissue	Decreased miR-195-5p expression was linked with poor prognosis.	Dong S. et al., 2019
35 pairs of GC and ACTs	Decreased miR-125a-5p expression was linked with poor prognosis.	Wang X. et al., 2019
52 pairs of CC and ACTs	Decreased miR-31-3p expression was linked with poor prognosis.	Jing et al., 2019
20 pairs of PCa and ACTs	Decreased miR-33a-5p expression was linked with poor prognosis.	Dai Y. et al., 2019
50 pairs of lung cancer and normal lung specimens	High expression of miR-548e-5p was linked with longer overall survival.	Jin et al., 2019
30 pairs of PCa and ACTs	High expression of miR-199b-5p was linked with poor prognosis.	Zhao et al., 2019
52 pairs of PCa and ACTs	High expression of miR-210-3p was linked with poor prognosis.	Ren et al., 2017
60 pairs of OC and ACTs	High expression of miR-1228 was linked with poor prognosis.	Du L. et al., 2020
36 pairs of tumor specimens and adjacent normal specimens	High expression of miR-127 was linked with poor prognosis.	Shi et al., 2017
20 pairs of RCC and ACTs	High expression of miR-452-5p was linked with poor prognosis.	Zhai et al., 2018
36 pairs of GBC and ACTs	Decreased miR-143-5p expression was linked with poor prognosis.	Taheri et al., 2017

carcinoma cells through regulation of the PI3K/AKT/mTOR signaling (Wang R. et al., 2020). In lung and esophageal cancers, MALAT1 exerts similar functions through modulating miR-124 expression and Ezh2/Notch1 axis, respectively (Chen et al., 2018; Wu et al., 2018). On the other hand, MEG3 enhances level of epithelial marker E-cadherin and suppresses mesenchymal markers vimentin and fibronectin in gastric carcinoma cells, indicating an anti-EMT function for this lncRNA (Jiao and Zhang, 2019). CCAT1 is an oncogenic lncRNA in cervical cancer cells whose silencing has blocked proliferation, migratory potential, invasiveness and EMT process in these cells. CCAT1 silencing has led to down-regulation of Runx2 and suppression of PI3K/AKT signaling in cervical cancer cells PI3K/AKT signal (Li et al., 2020a). HAL is a down-regulated lncRNA in serous ovarian cancer tissues and cells. Up-regulation of HAL has suppressed invasive potential of these cells and enhanced their apoptosis. HAL has been shown to directly suppress expression of TWIST1. Functional studies has highlighted the role of HAL in regulation of EMT (Wu K. et al., 2020). In ovarian cancer, LINC00963, TC0101441, CCAT1 and PTAR promote EMT through modulation of miR-378g, KiSS1, miR-490-3p and miR-101-3p, respectively (Liang et al., 2018; Mu et al., 2018; Liu et al., 2020; Qiu et al., 2020). **Supplementary Table 2** summarizes the functions of EMT-associated lncRNAs in human cancers.

Epithelial to mesenchymal transition-associated lncRNAs have both diagnostic and prognostic values in cancer patients. For example, expression levels of GHET1 could differentiate cancer and normal esophageal tissues with high accuracy (Liu H. et al., 2017). Over-expression of LINC00963, FLVCR1-AS1 and LINC00261 has been associated with poor overall survival rate of patients with neoplasm (Yan et al., 2019; Gao et al., 2020; Liu et al., 2020). **Table 2** summarizes the results of studies that report diagnostic and prognostic roles of EMT-associated lncRNAs in cancer.

DISCUSSION

Numerous miRNAs and lncRNAs have been shown to regulate EMT process. These ncRNAs participate in this process through influencing activity of several signaling pathways such as NF-κB, TGF-β, Wnt/β-catenin, Akt/mTOR, PIK3R3 and EGFR. The Wnt/β-catenin pathway is the target of several miRNAs such as miR-6838-5p, miR-770, miR-23a, miR-27a, miR-125b, miR-375, miR−516a−3p, miR-630, miR-330-3p, miR-147, miR-138 and miR-3622a-3p. Moreover, lncRNAs UCA1, SNHG7, GATA6-AS1, CRNDE and FEZF1-AS1 exert their regulatory roles on EMT through modulation of this signaling pathway. Thus, the Wnt/β-catenin pathway can be regarded as a focal point for organization of EMT-associated ncRNAs. This important position potentiates this pathway as a therapeutic target in reversing the EMT process. As the Wnt/β-catenin pathway has been implicated in the progression of EMT during tumor evolution (Basu et al., 2018), it is predicted that ncRNAs

TABLE 2 | Diagnostic and prognostic role of EMT-associated lncRNAs in cancer (ACTs: adjacent control tissues, OS: overall survival).

Sample number	Area under curve	Sensitivity	Specificity	Kaplan-Meier analysis	Multivariate cox regression	References
35 pairs of OS and ACTs	-	-	-	High expression of LINC00963 was linked with poor overall survival rate.	High expression of LINC00963 was associated with metastasis rate of lymph nodes and FIGO stage	Liu et al., 2020
50 pairs of SOC and ACTs	-	-	-	High expression of FLVCR1-AS1 was linked with poor OS.	High expression of FLVCR1-AS1 was associated with lymphatic metastasis and distant metastasis.	Yan et al., 2019
50 pairs of CCA and ACTs	-	-	-	High expression of LINC00261 was linked with poor OS.	High expression of LINC00261 was associated with large tumor size, positive lymph node metastasis, advanced TNM stages, and higher post-operative recurrence.	Gao et al., 2020
76 pairs of GC and ACTs	-	-	-	High expression of TP73-AS1 was linked with poor OS.	High expression of TP73-AS1 was associated with depth of invasion and TNM stages.	Zhang et al., 2018c
18 pairs of GC and ACTs	-	-	-	Low expression of HRCEG was linked with poor OS.	-	Wu Q. et al., 2020
162 pairs of GC and ACTs	-	-	-	High expression of SNHG7 was linked with poor OS.	High expression of SNHG7 was associated with TNM stage, depth of invasion, lymph-node metastasis, and distant metastasis.	Wu S. et al., 2020
84 pairs of GC and ACTs	-	-	-	High expression of HCP5 was linked with poor OS.	High expression of HCP5 was associated with the size of the tumor, lymph nodes metastasize, and the severity of the disease	Zhang et al., 2020
78 pairs of GC and ACTs	-	-	-	High expression of SNHG6 was linked with poor OS.	High expression of SNHG6 was associated with invasion depth, lymph node metastasis, distant metastasis, and TNM stage.	Yan et al., 2017
92 pairs of CRC and ACTs	-	-	-	High expression of HIF1A-AS2 was linked with poor OS.	High expression of HIF1A-AS2 was associated with TNM stages.	Lin et al., 2018
338 pairs of CRC and ACTs	-	-	-	High expression of SNHG1 was linked with poor OS.	-	Bai et al., 2020
124 pairs of CRC and ACTs	-	-	-	High expression of PANDAR was linked with poor OS.	High expression of PANDAR was associated with tumor diameter, histological differentiation, TNM stage, lymph node metastasis, depth of invasion.	Lu et al., 2017
76 pairs of CRC and ACTs	-	-	-	High expression of TUG1 was linked with poor OS.	-	Sun et al., 2018
82 pairs of BC and ACTs	-	-	-	High expression of TP73-AS1 was linked with poor OS.	-	Ding et al., 2019
TCGA database	-	-	-	High expression of PVT1 was linked with poor OS.	-	Chang et al., 2018
40 pairs of HC and ACTs	-	-	-	High expression of SNHG7 was linked with poor OS.	-	Yao et al., 2019
134 pairs of HCC and ACTs	-	-	-	High expression of SBF2-AS1 was linked with poor OS.	High expression of SBF2-AS1was associated with vein invasion and TNM stage.	Zhang et al., 2018e
54 pairs of HCC and ACTs	-	-	-	High expression of LOC105372579 was linked with poor OS.	High expression of LOC105372579 was associated with tumor size and TNM stage.	Changyong et al., 2019
HCC tissues (n = 38), normal liver tissues (n = 21)	-	-	-	High expression of HULC was linked with poor OS.	High expression of HULC was associated with clinical stage and intrahepatic metastases.	Li et al., 2016
76 pairs of HCC and ACTs	-	-	-	High expression of HOXA−AS3 was linked with poor OS.	-	Tong et al., 2019
76 pairs of OSCC and ACTs	-	-	-	High expression of ADAMTS9-AS2 was linked with poor OS.	High expression of ADAMTS9-AS2 was associated with tumor size, clinical stage, and lymph node metastasis.	Li Y. et al., 2019

(Continued)

TABLE 2 | Continued

Sample number	Area under curve	Sensitivity	Specificity	Kaplan-Meier analysis	Multivariate cox regression	References
123 OSCC tissues and 50 adjacent non-tumor tissues	-	-	-	High expression of H19 was linked with poor OS.	-	Zhang et al., 2017a
128 pairs of BLC and ACTs	-	-	-	High expression of TP73-AS1 was linked with poor OS and PSF rates.	-	Tuo et al., 2018
48 pairs of NPC and ACTs	-	-	-	High expression of TUG1 was linked with poor OS.	-	Qian et al., 2019
42 pairs of BLC and ACTs	-	-	-	High expression of NRON was linked with poor OS.	High expression of NRON was associated with tumor invasion depth.	Xiong et al., 2020
30 pairs of OS and ACTs	-	-	-	High expression of PCAT1 was linked with poor OS.	High expression of PCAT1 was associated with advanced clinical-stage and tumor metastasis.	Zhang et al., 2018d
305 pairs of LUAD and ACTs	-	-	-	High expression of H19 was linked with poor OS.	High expression of H19 was associated with tumor diameter and TNM stage.	Liu et al., 2019
107 pairs of LUAD and ACTs	-	-	-	High expression of TTN-AS1 was linked with poor OS.	High expression of TTN-AS1 was associated with TNM stage and lymph node involvement.	Jia et al., 2019
50 pairs of NSCLC and ACTs	-	-	-	Low expression of NBR2 was linked with poor OS rate.	-	Gao et al., 2019
86 pairs of NSCLC and ACTs	-	-	-	High expression of FEZF1-AS1 was linked with poor OS.	High expression of FEZF1-AS1 was associated with lymph node metastasis, poor differentiation grade, and advanced TNM stage.	He et al., 2017
55 pairs of ESCC and ACTs	0.858	69.7%	91.3%	Low expression of GHET1 was linked with poor OS.	High expression of GHET1 was associated with lymph node metastasis, differentiation, and TNM stage.	Liu H. et al., 2017
25 pairs of RCC and ACTs	-	-	-	High expression of PVT1 was linked with poor OS.	High expression of PVT1 was associated with TNM stage, fuhrman grade, lymph node involvement, and tumor dimension.	Ren et al., 2019

contribute to the fine-tuning of activity of this pathway to confer different degrees of EMT.

Circular RNAs are another group of ncRNAs that participate in carcinogenesis (Su et al., 2019). However, their role in the EMT process has been less studied. High−throughput transcript sequencing as a new method can be applied to identify EMT-associated circRNAs. This strategy has led to identification of 7 up-regulated circRNAs and 16 down-regulated circRNAs in breast cancer cells with EMT phenotype. CircSCYL2 has been among under-expressed circRNAs in breast cancer tissues and cell lines. Up-regulation of circSCYL2 has suppressed migration and invasion (Yuan et al., 2020).

Several therapeutic modalities such as short hairpin RNAs and engineered antibodies have been designed to reverse the EMT process in cancer cells. Moreover, a number of natural agents have been demonstrated to suppress EMT through modulation of the important EMT-associated molecules or pathways (Loh et al., 2019). NcRNAs have been involved in the therapeutic efficiency of both conventional and natural anticancer drugs (Dong Y. et al., 2019; Tao et al., 2020). Thus, modulation of expression of EMT-associated ncRNAs is a promising strategy for enhancement of the response of patients to anti-cancer drugs.

Expression levels of EMT-associated miRNAs and lncRNAs has been linked to the survival of cancer patients. Therefore, it is possible that a panel of EMT-associated miRNAs and lncRNAs predict disease progression and therapeutic response with clinically relevant accuracy. However, there is no consensus set of ncRNAs to facilitate the design of such diagnostic tools as yet. Thus, future studies should focus on the integration of data provided by single studies to propose a diagnostic/prognostic panel consisting of EMT-associated lncRNAs and miRNAs. As discussed above, lncRNAs and miRNAs have functional interactions to modulate EMT. System biology methods are useful in recognition of such interactions and depicting the interaction network to identify the most important modules. Identification of these modules not only facilitates design of diagnostic panels, but also help in design of targeted therapies. Systems biology methods have been successfully used to integrate modeling and experimental data, leading to identification of several intermediate states participating in the EMT process (Hong et al., 2015). Moreover, construction of model of the miRNA-based coupled chimeric modules has led to identification of the role of miR-200/ZEB module in switching between epithelial and mesenchymal features and in establishment of a hybrid phenotype with assorted features of collective cell

migration, as documented in physiological processes (Lu et al., 2013). Moreover, system biology methods have been used to find the main regulatory network which controls TGF-β-induced EMT (Tian et al., 2013).

Taken together, ncRNAs are associated with important features in invasive and metastatic cancers, i.e., the EMT process. Therapeutic interventions that modulate expression of these transcripts can improve survival of cancer patients.

Although the role of ncRNAs in regulation of EMT in cancer has been extensively appraised, less is known about their contribution in the regulation of this process in non-cancerous context.

AUTHOR CONTRIBUTIONS

MT and SG-F wrote the draft and revised it. HS, MM, MD, and HH collected the data, designed the tables and figures. All the authors approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmolb.2021.665199/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.