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 allows polarized epithelial cells 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 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 studied 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 this 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

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 (IncRNAs) 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 HMG2 levels and poor clinical outcome. Stable up-regulation of miR-330 in these cell lines has decreased HMG2 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 colorectal cancer, miR-145-5p, miR-3622a-3p, miR-205 and miR-200b inhibit EMT through targeting CDCA3, SALL4, MDM4 and HIF-1α, respectively (Shang et al., 2017; 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, miR-99a and miR-92b is linked with prolonged survival in lung...
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.

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
Numerous miRNAs and lncRNAs have been shown to regulate EMT process 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 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 underexpressed circRNAs in breast cancer tissues and cell lines. Up-regulation of circSCYL2 has suppressed migration and invasion (Yuan et al., 2020).

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

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

| Sample number | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Multivariate cox regression | References |
|---------------|------------------|-------------|-------------|------------------------|-----------------------------|------------|
| 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 |
| 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-AS1 was 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 |
| 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 |

(Continued)
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.

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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.

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