Tumor Microenvironment and Noncoding RNAs as Co-drivers of Epithelial–Mesenchymal Transition and Cancer Metastasis

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Reciprocal interactions between cancer cells and tumor microenvironment (TME) are crucial events in tumor progression and metastasis. Pervasive stromal reprogramming of TME modifies numerous cellular functions, including extracellular matrix (ECM) stiffness, inflammation, and immunity. These environmental factors allow selection of more aggressive cells that develop adaptive strategies associating plasticity and epithelial-mesenchymal transition (EMT), stem-like phenotype, invasion, immunosuppression, and resistance to therapies. EMT is a morphomolecular process that endows epithelial tumor cells with mesenchymal properties, including reduced adhesion and increased motility. Numerous studies have demonstrated involvement of noncoding RNAs (ncRNAs), such as miRNAs and lncRNAs, in tumor initiation, progression, and metastasis. NcRNAs regulate every hallmark of cancer and have now emerged as new players in induction and regulation of EMT. The reciprocal regulatory interactions between ncRNAs, TME components, and cancer cells increase the complexity of gene expression and protein translation in cancer. Thus, deeper understanding of molecular mechanisms controlling EMT will not only shed light on metastatic processes of cancer cells, but enhance development of new therapies targeting metastasis. In this review, we will provide recent findings on the role of known ncRNAs relevant to EMT and cancer metastasis and discuss the role of the interaction between ncRNAs and TME as co-drivers of EMT.

Introduction

Malignant tumors are highly heterogeneous tissues represented by cancer cells and tumor microenvironment (TME) composed of non-tumoral cells and modified extracellular matrix (ECM). Pervasive TME remodeling and reprogramming modify numerous physical, biochemical, and stromal cell functions, including pH, oxidative stress, ECM stiffness, metabolism, inflammation, and immunity. Simultaneously, cancer cells develop important adaptive strategies to adjust their phenotype to unfavorable environmental conditions. Subsequently, heterogeneous subpopulations of cancer cells acquire new properties associating plasticity, stem-like phenotype, metabolic reprogramming, invasion, immunosuppression, and therapeutic resistance (Meseure et al., 2014).

These transformations represent the epitome of dynamic tumor cell behavior.

Cellular plasticity includes multistep morphogenetic and biological mechanisms elicited by cancer cells to govern tumor progression, metastatic spread, and response to therapies. The most widely known plasticity processes are the epithelial–mesenchymal transition (EMT) and the mesenchymal–epithelial transition (MET), which are fundamental reversible mechanisms (Nakaya and Sheng, 2013). EMT was first described in embryogenesis and in formation of various tissues or organs. Cancer cells follow similar EMT process to establish metastases. EMT facilitates epithelial cancer cells to enter into a mesenchymal-like state by endowing the migratory and invasive properties, which enables a primary tumor to move and colonize distant organs and form metastases. EMT is a critical step in the early phase of cancer metastasis and is closely linked to carcinogenesis.
invasion, recurrence, and therapy resistance. In recent years, there has been a shift in scientific focus on the field of tumor progression and metastasis.

Large-scale genomic technologies (high-resolution microarray, whole genome, and RNA sequencing) combined with bioinformatics analyses have profoundly changed the genome organization understanding. Unexpectedly, these global transcriptional analyses revealed that 80% of the genome is transcribed and presents biochemical marks of active transcription, whereas less than 2% encodes proteins (Meseure et al., 2016a). Discovery of a “second genetic code” consisting of non-coding RNAs (ncRNAs) has changed the traditional concept of genomic organization characterized by the presence of genes encoding islets scattered in a sea of repeats and non-transcribed proteins. Moreover, Encyclopedia of DNA elements (ENCODE) analysis recently revealed that only 56 of 41,204 genes (0.1%) showed mass spectrometric evidence consistent with protein expression, suggesting that the majority of ribonucleic acid (RNA) transcripts are ncRNAs (Bernstein et al., 2012). This large population of ncRNA transcripts indicates that RNAs have a larger and more diverse role than initially believed. Emerging evidence has revealed that ncRNAs are frequently regulated in various diseases, especially in carcinogenesis, and have an important role in cancer progression. Recent studies have also demonstrated an essential role of ncRNAs in regulating EMT and cancer metastasis. NcRNAs can be classified into two major groups based on their transcript size. The first group is the small RNAs, less than 200 nucleotides (nt) in length, which includes principally the well-known microRNAs (miRNAs; ~22nt). The second group includes long ncRNAs (lncRNAs; ≥200 nt). NcRNAs such as mRNA, small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), circular RNAs, and lncRNAs have critical regulatory roles in gene expression (Fang and Fullwood, 2016).

MiRNAs normally direct RNA-induced silencing complex to the 3’UTR of target genes and regulate their expression. They can modulate gene transcription rates, inhibit the initiation and elongation of translation of target messenger RNAs (mRNAs), promote target mRNA decay, and reduce stability of proteins newly synthesized from target mRNAs. They can also sequester target mRNAs in cytoplasmic regions (P-bodies) where translation and stability are diminished (Yoon et al., 2014). MiRNAs can act in solo or as clusters of two or more miRNAs that jointly regulate molecular pathways either by co-targeting individual genes or by targeting different components of the same pathway (Haussler et al., 2014). MiRNAs can function as either oncogenes or tumor suppressors. MiRNAs have also emerged as crucial mediators of intercellular communication, based on cell-derived extracellular exosomes (Soon and Kiaris, 2013). Mounting evidence has demonstrated that miRNAs take part in all stages and aspects of cancer cell development, adhesion, differentiation, EMT, apoptosis, and metabolism.

LncRNAs, as a newer class of ncRNAs, are divided into five broad categories with respect to the nearest protein-coding transcripts: sense, antisense, bidirectional, intronic, and intergenic. LncRNAs disclose a new understanding of gene expression in cancers. LncRNAs can act in cis or trans to modulate gene expression, by binding miRNAs to protect messenger RNAs (mRNAs) as endogenic competitors, or through regulating gene expression by multiple molecular mechanisms at epigenetic, transcriptional, and post-transcriptional levels (Xu et al., 2016b). Increasing evidence has demonstrated a potential role of lncRNAs in tumor metastasis by influencing EMT. Furthermore, there are growing interests in using lncRNAs as prognostic biomarkers and potential therapeutic targets (Meseure et al., 2015).

Recently, functional interactions between lncRNAs and miRNAs have come into view. LncRNAs are targeted by miRNAs to reduce their stability. LncRNAs function as molecular decoys or sponges of microRNAs. They also compete with miRNAs for binding to shared target miRNAs and are precursors for the generation of miRNAs to silence target mRNAs (Yoon et al., 2014).

Overall, EMT is regulated by a complex signaling network at epigenetic, transcriptional, and post-transcriptional levels, including molecular pathways, transcription factors (TFs), and ncRNAs. Additionally, various microenvironment factors like mechanical stresses, hypoxia, and ECM stiffness can also act as powerful mediators of EMT and tumor invasion (Diepenburk et al., 2016). Therefore, deeper understanding of molecular mechanisms controlling EMT will not only shed light on metastatic processes of cancer cells, but also enhance development of new therapies targeting factors driving metastasis, which remains a crucial goal for both physicians and scientists.

In this review, we will provide recent findings on the role of known ncRNAs relevant to EMT and cancer metastasis, and we will discuss the role of the interaction between these ncRNAs and tumor microenvironment as co-drivers of cancer cells EMT and cancer metastasis.

**Role of Microenvironment and ncRNAs in Tumor Progression, EMT, and Metastasis**

Cancer cells need cellular, biochemical, and biophysical stimuli originating from a more adapted microenvironment by recruiting and educating various types of cells into their neighborhood (Fulda, 2010). Development of a tumorogenic microenvironment is driven by genetic instability of cancer cells and by epigenetic factors in response to exogenous and endogenous stress stimuli. Exogenous factors include hypoxia, aberrant angiogenesis, acidosis, glucose deprivation, oxidative stress, and pH changes. Endogenous stressors associate imbalanced cell growth, increased mutation rate, errors in glycoprotein and lipid biosynthesis, and decreased amino acid supplies (Mahadevan and Zanetti, 2011). The tumor stromal–inflammatory interface represents a dynamic space, within exchange of numerous molecular information associated with stromal and cancer cell transitions and includes growth factors (GFs), cytokines, chemokines, enzymes, matrix metalloproteinases (MMPs), and metabolic intermediates. Recruitment, activation, reprogramming, and persistence of inflammatory and stromal cells in the extracellular space are the consequences of a reciprocal relationship between TME and cancer cells (Meseure et al., 2014). Reciprocal interactions between cancer cells and TME are crucial in selecting cancer cell subpopulations with more aggressive properties. Additionally, cancer cells may interact with and modify stromal cellular functions by using a specific program resulting in cancer-associated alternated splicing events (Brosseau et al., 2013). Consequently, some cancer cells acquire EMT properties to govern immunosuppression, tumor progression, metastasis, and therapeutic resistance (Meseure et al., 2014).

Growing evidence indicates that EMT is induced by different biological mechanisms and that the mutual interaction between cancer cells and the surrounding TME is a crucial step supporting the entire EMT process (Bottai et al., 2016). Recently, EMT has been reported to be regulated by post-transcription factors, such
as miRNAs and lncRNAs, which can influence and regulate effectors, TFs, and signaling pathways (Cao et al., 2017). Reciprocally, miRNAs and lncRNAs interact with TME components such as ECM, cancer associated fibroblasts (CAFs), angiogenesis, inflammation, hypoxia, and reactive oxygen species (ROS), which in turn influence EMT process.

**Intercellular communication**

Intercellular communication serves as the basis for functional coordination between cells in multicellular organisms. The signaling pathways associated are based on different mechanisms, such as direct cell-to-cell contact, indirect communication by release of soluble factors or vesicles, or non-contact communication (Scholkmann et al., 2013; Chaban et al., 2013). This process is based on cell-derived extracellular vesicles (EVs). EV components associate transmembrane proteins, lipids, DNA, mRNA, and ncRNAs, including miRNAs. Generally, EVs are subdivided into three groups of particles according to their size: exosomes (30–200 nm), ectosomes or shedding microvesicles (100–1000 nm), and large oncosomes (1–10 μm) (Raposo and Stoorvogel, 2013). Stromal stressors like acidosis and hypoxia act by modulating EV molecular content, secretion, trafficking, and activity. EVs are implicated in tumor progression mechanisms, including ECM degradation, angiogenesis, escape to immune surveillance, metastatic spread, and therapy resistance (Meseure et al., 2014).

MiRNAs can be transferred by exosomes from a donor to a recipient cell in order to modulate gene expression (Valadi et al., 2007; Paladini et al., 2016). Exosomes can be produced by different types of cells, including stromal, immune cells, and tumor cells. Moreover, exosome-derived miRNAs act as mediators of intercellular communication occurring between different types of cells within TME. Therefore, cancer-secreted miRNAs may play a crucial role in regulating various cellular components of TME in order to facilitate metastasis.

Exosomes also influence cancer cells’ epithelial-mesenchymal plasticity. Recent data revealed that SMAD4 mutations and up-regulation of miR-21 perpetuate an EMT phenotype in ovarian cancer cells and enhance chemoresistance profile by exosomal exchange. This mechanism provides a novel insight as to how tumor-derived exosomal transfer enhances EMT in response to chemotherapy (Crow et al., 2017). In contrast, prostate cancer cell–derived exosomes, including oncogenic miR-125b, miR-130b, and miR-155, can influence neoplastic reprogramming and tumor progression by inducing MET of mesenchymal stem cells (MSCs) (Abd Elmageed et al., 2014).

Furthermore, tumor-derived exosomes can alter ECM through secretion or activation of MMPs. Subsequently, MMPs can degrade ECM proteins, such as collagen, fibronectin, proteoglycans, and laminins, which in turn influence cancer cell mobility and invasion (Hanahan and Weinberg, 2011; Paladini et al., 2016). In addition, miR-105 secreted by breast cancer cells can be transferred to endothelial cells via exosomes. Then, exosomal miR-105 induces vascular permeability and promotes metastasis by targeting tight junction protein zonula occludin-1 (ZO-1) in endothelial cells (Zhou et al., 2014b).

**Cell-cell adhesion and cytoskeletal dynamic molecules**

In normal epithelial cells, adherens and tight junctions comprise two modes of cell-cell adhesion. Both junctional complexes are proposed to associate with actin cytoskeleton. Adheren junctions consist of the transmembrane protein E-cadherin and intracellular components, p120-catenin, β-catenin, and α-catenin. The adheren junction performs multiple functions including initiation and stabilization of cell–cell adhesion, intracellular signaling, and transcriptional regulation. Tight junctions consist of the transmembrane proteins occludin and claudin, as well as the cytoplasmic scaffolding zonula occludin proteins ZO-1, ZO-2, and ZO-3. Tight junctions regulate the paracellular pathway for the movement of ions and solutes in between cells (Hartsock and Nelson, 2008). The actin cytoskeleton is a highly dynamic entity, and even subtle perturbation of the rates of actin polymerization and depolymerization can cause dramatic changes in cellular behavior (Valastyan and Weinberg, 2011). Consequently, cytoskeletal dynamics are tightly controlled under normal physiological settings (Parsons et al., 2010). One central control node that oversees actin polymerization and depolymerization is composed of members of the Rho superfamily of small GTPases, which encompasses the Rho, Rac, and Cdc42 subfamilies (Heasman and Ridley, 2008). The Rho signaling can be controlled at the level of expression of downstream effectors of the small GTPases (Parsons et al., 2010). There are three Rho GTPases in human: RhoA, RhoB, and RhoC. RhoA plays key roles in the regulation of actomyosin contractility, as well as in cell proliferation and survival. The behavior of actomyosin critically determines morphologically distinct patterns of contractility found at the interface between adherent cells. RhoB, which is localized primarily on endosomes, has been shown to regulate cytokine trafficking and cell survival. RhoC plays a major role in the regulation of actin cytoskeleton, cell shape, attachment, and motility, which is highly relevant to cancer metastasis. Rho GTPases carry out these distinct functions by activating various downstream effectors, including Rho kinase 1 (ROCK1) and Rho kinase 2 (ROCK2) (Jiang et al., 2010a). An experimentally induced decrease in E-cadherin expression by siRNA causes a delay in correct localization of α-catenin, β-catenin, and ZO-1 (Capaldo et al., 2007). Loss of E-cadherin had a reproducible effect on morphology of epithelial cells. At low density of E-cadherin, apical cell surfaces become domed, and epithelial cells seem more fibroblastic and migrate more rapidly, consistent with reduced adhesiveness (Qin et al., 2005; Capaldo et al., 2007).

MiRNAs targeting cellular adhesion and cytoskeletal dynamic molecules. MiRNAs can promote EMT by interaction with cellular adhesion and cytoskeletal dynamic molecules. Emerging evidence revealed that miRNAs are likely to play a fundamental role in all aspects of cellular adhesion signal transduction by regulating cellular adhesion pathways or by suppressing expression of various proteins belonging to the cell adhesion system, including cytoskeletal regulatory proteins, cell-cell adhesion molecules, cell-matrix adhesion molecules, and ECM proteins collagen and fibronectin (Parsons et al., 2010). At a molecular level, miRNAs appear to affect cancer progression by regulating numerous miRNAs that encode proteins with functions in cell-adhesion processes, such as RhoC, RhoA, E-cadherin, and tenasin C (Valastyan and Weinberg, 2009a). Certain miRNAs target mRNA-encoding members of the Rho superfamily. MiR-31, miR-133, and miR-155 suppress expression levels of RhoA in various tissue types (Valastyan and Weinberg, 2010; Cáre et al., 2007; Kong et al., 2008). In cancer cells, miR-10b induced by transcription factor Twist inhibits translation of mRNA-encoding homeobox D10, resulting in increased expression of prometastatic gene.
RHOC (Ma et al., 2007). In contrast, miR-138 plays an important role in cancer cell migration and invasion by reducing expression of RHOC (Jiang et al., 2010a). Moreover, Rho downstream effector ROCK2 can be targeted by both miR-138 and miR-139 (Jiang et al., 2010a; Wong et al., 2011). Interestingly, miR-133 simultaneously suppresses expression levels of two GTPases, RhoA and Cdc42, that play fundamental roles in controlling cytoskeletal dynamics. Expression of Cdc42 can also be suppressed by miR-29 and miR-224 (Park et al., 2009; Càre et al., 2007; Zhu et al., 2010). Additionally, it seems that miRNAs play a crucial role in overseeing post-translational regulatory events of Rho family. For example, Tiam1, a Rac guanine nucleotide exchange factor (GEF), is a downstream effector of miR-10b (Morearty et al., 2010). Analogously, miR-151 can target the mRNA-encoding RhoGDIA (Ding et al., 2010). Furthermore, the miR-200 family can coordinately target both cell-cell adhesion molecules and cytoskeletal regulatory proteins (Valastyan and Weinberg, 2011). Thus, miRNAs can impact small GTPase signal transduction at multiple distinct nodes of intervention.

The activities of many adhesion-related miRNAs or cytoskeletal regulatory proteins have been found to be altered during tumor development and subsequent metastatic progression (Valastyan and Weinberg, 2011). The miR-17/92 cluster is a well-characterized family of known oncogenic miRNAs, whereas the let-7 seed family functions as a classical tumor suppressor gene in many tumor types (Ventura and Jacks, 2009). Similarly, several additional miRNAs involved in regulating cell adhesion, such as miR-10b, miR-31, miR-200, and miR-335, have been found to contribute causally to various aspects of metastatic progression (Valastyan and Weinberg, 2009b).

When taken together, the recent above-cited data provide evidence of the effects of miRNAs on cellular phenotypes by interaction with cell adhesion–related signal and molecules and prove that altered activity of these ncRNAs in cancer contributes crucially to tumor progression, EMT, and metastasis.

**Stromal cells**

CAF s represent a heterogeneous population of three main cell types: fibroblasts, myofibroblasts, and cancer-associated adipocytes. They are activated in response to TGFβ produced by adjacent cancer cells (Zhang et al., 2013a). In turn, CAFs play key roles in all stages of tumor progression by issuing numerous oncogenic cytokines (IL-1, IL-6, IL-8), chemokines (CXC chemokines CXCL1 to CXCL12, CC chemokines CCL2 and CCL20), ECM proteins (fibronectin, collagen I and III, EDA-fibropectin, tenascin C, and SPARC), enzymes (MMP-1, MMP-2, MMP-7, MMP-9, MMP-13, MMP-14; LOX family oxidases and LOX-like proteins 1–4), and COX2 (Tjomsland et al., 2010). CAFs secrete various growth factors, including hepatocyte growth factor (HGF), insulin-like growth factors (IGFs), nerve growth factor (NGF), wingless-type MMTV integration site family member 1 (WNT1), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). PDGF/platelet-derived growth factor receptors (PDGFR) axis is of paramount importance as master regulator of respectively normal and cancer cell trafficking and of TME development (Teicher et al., 2010; Anderberg et al., 2009). CAFs are partly responsible for cancer-associated inflammation and de novo angiogenesis. They secrete stromal cell–derived factor 1 (SDF1), which stimulates tumor angiogenesis by recruiting endothelial progenitor cells and enhances tumor cell proliferation through its interaction with the CXCR4 receptor expressed by epithelial cancer cells (Orimo and Weinberg, 2006). CAFs are instrumental in ECM remodeling that alters its composition via excess of EDA-fibropectin, tenascin C, and SPARC. These protumoral matrix proteins make ECM more permissive for cancer cell invasion and play a complementary role to that of MMPs secreted by cancer cells. CAFs are also implicated in ECM stiffness and fibrosis via deposition of collagen type I. In addition, CAFs play a central role in collective migration by serving as leader cells to cancer cells and by promoting development of invasion paths via collagen arranged perpendicularly to tumor cells. This reorganization is based on activity of MMPs, integrins, and their connections with actin cytoskeleton that generate contractile forces. CAFs force a malignant cross talk with cancer cells, culminating in their EMT and achievement of stemness traits (Comito et al., 2014).

Reciprocal interactions between miRNAs and stromal cells. MiRNAs interact with stromal components and promote tumor cell EMT, migration and invasion. Interactions between miRNAs, normal fibroblasts, and CAFs have been recently identified. Overexpression of the hypoxia–induced miR-210 or muscle-specific miR-133b in fibroblasts converts them into CAFs able to promote prostate cancer cells EMT (Taddei et al., 2014; Doldi et al., 2015). A set of 3 miRNAs (miR-214, miR-31, and miR-155) reprogram normal fibroblasts to CAFs in ovarian cancer. Downregulation of miR-214 and miR-31 and up-regulation of miR-155 trigger reprogramming of quiescent fibroblasts to CAFs. MiR-214 has also an inverse correlation with its chemokine target CCL5. As expected, reverse regulation of these miRNAs reduces migration, invasion, and colony formation of co-cultured ovarian cancer cells (Mitra et al., 2012). In breast cancer patients, low miR-126 expression has been shown to correlate with poor metastasis-free survival due to stromal cell recruitment (Zhang et al., 2013b). In endometrial cancer, miR-31 directly targets the homeobox gene SATB2, which is responsible for chromatin remodeling and regulation of gene expression, and is significantly elevated in CAFs. Overexpression of miR-31 significantly impaired the ability of CAFs to stimulate tumor cell migration and invasion without affecting tumor cell proliferation. Genetic manipulation of SATB2 levels in normal fibroblasts or CAFs showed that, reciprocally to miR-31, SATB2 increased tumor cell migration and invasion, while knockdown of endogenous SATB2 in CAFs reversed this phenotype. These findings provide new insights into tumor-stroma interactions and document that miR-31 and its target gene SATB2 are involved in regulation of tumor cell motility (Aprelikova et al., 2010). Additionally, miR-148a has shown to be down-regulated in CAFs from patients with endometrial cancer, with up-regulation of WNT10B that has been identified as a direct target of miR-148a in CAFs, and its up-regulation increases cancer cell motility (Aprelikova et al., 2013). In gastric cancer, miR149 links prostaglandin E2 (PGE2) and IL-6 signaling in mediating the cross talk between cancer cells and CAFs. Then CAFs enhance EMT and stem-like properties of cancer cells in a miR-149-IL-6–dependent manner. Furthermore, *Helicobacter pylori* infection, a leading cause of human gastric carcinoma, is able to induce COX2/PGE2 signaling and enhance PGE2 production, resulting in the hypermethylation of miR-149 in CAFs and increased IL-6 secretion (Li et al., 2015a). Further, miR–21 up-regulation occurs predominantly in CAFs in breast, lung, colon, and
esophageal cancers, and has been shown to contribute to inducing the CAF phenotype and increase the invasiveness and migration of the associated cancer cells (Nouraei et al., 2013). In comparison, miR-101 is notably down-regulated in CAFs, causing increased expression of CXCL12 affecting migration and invasiveness of lung cancer cells (Zhang et al., 2015a). In addition, repression of phosphatase and tensin homolog (PTEN) expression in CAFs leads to down-regulation of miR-320 and up-regulation of its oncogene target ETS2, inducing a pro-oncogenic environment (Khew-Goodall and Goodall, 2012). Suppressed miR-126/126* levels lead to increased levels of both SDF1α and CCL2, thereby promoting cancer cell proliferation and recruitment of MSCs and inflammatory monocytes in TME (Zhang et al., 2013b). Decreased levels of miR-15a/miR16-1 cluster led to decreased post-transcriptional repression of FGF-2 and FGFR-1, causing enhanced cancer cell survival in prostate cancer (Musumeci et al., 2011). Thus, miR-15a and miR-16-1 act as putative tumor suppressors, and when significantly decreased, lead to decreased levels of BCL2, CCND1 (encoding cyclin D1), and WNT3A (Bonci et al., 2008). Comparatively, miR-26b, which is commonly down-regulated in CAFs, is a potent regulator of cancer behavior in estrogen receptor (ER)-positive breast cancer. Reduced miR-26b in cancer stroma can stimulate migration and invasion of epithelial cancer cells in the context of epithelial/fibroblast co-cultures by targeting type XII collagen a1 expression, and this, in turn is significantly associated with breast cancer recurrence (Verghese et al., 2013).

Reciprocal interactions between lncRNAs and stromal cells. Several lncRNAs have been reported to interact with stromal components. Previous studies showed a preferential expression of MEG3 and H19 in tumor stroma (Zhang et al., 2016; Adriaenssens et al., 1998). Interestingly, A recent transcriptomic analysis of breast carcinomas revealed a high correlation between six ECM-associated lncRNAs (LINC00922, RP11-38H17.1, RP11-400N13.3, RP11-417E7.2, RP11-863P13.3, and RP5-1172A22.1) and CAF markers FAP and ACTA2. This correlation suggests a role of lncRNAs in acquisition of an activated phenotype by fibroblasts in the TME (Bradford et al., 2016). Although mechanisms in which lncRNAs activate fibroblasts are still poorly understood, the possibility that numerous lncRNAs may have a role in their regulation opens up an enticing research opportunity.

**Immune/inflammatory cells**

Inflammation is now acknowledged as an important hallmark of cancer. TME contains higher densities of immune and inflammatory cells than normal tissues, including dendritic cells (DCs), various subpopulations of lymphoid cells (T and B lymphocytes), natural killer (NK) cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). Inflammatory cells infiltrate tumor tissue via a network of cytokines and chemokines produced by cancer cells that reprogram and activate immune and inflammatory cells.

Lymphocytes play a critical role in tumor progression and metastasis (Zamarron and Chen, 2011). Over the past years, T cells (CD3, CD4, CD8, FOXP3, and rations between these), the so-called tumor infiltrating lymphocytes (TILs), have been studied intensively (Hadrup et al., 2013). However, the type and functional status of TILs and their microenvironment localization can determine the balance between control and promotion of cancer (Fridman et al., 2012). A meta-analysis study of several cancer types revealed that the presence of CD3+ and CD8+, as well as a high CD8+/FOXP3+ ratio in TME, had a positive effect on survival (Gooden et al., 2011). In breast cancer, the prognostic value of FOXP3 + regulatory TIL differs depending on ER and human epidermal growth factor receptor 2 (HER2) status and CD8 + cytotoxic T-cell infiltration. FOXP3+ TILs are a favorable prognostic factor and robust antitumor immunity in the HER2+/ER- subtype, but a poor prognostic indicator in ER+ breast cancer (Liu et al., 2014). Moreover, FOXP3+ TILs are positively correlated with CD8+ infiltration. Additionally, most FOXP3+ TILs in triple-negative breast cancer display a conventional CD4+/CD25+ Treg phenotype (West et al., 2013). In contrast, recent data indicate that FOXP3 could be expressed in several tumor cells and involved in the interaction between tumor cells and lymphocytes. In gastric cancer, the high expression of FOXP3 in tumor cells predicts better survival (Ma et al., 2014).

Whereas cytotoxic CD8+ and CD4+ T-helper 1 (Th1) cells function as major antitumor immune effector cells, CD4 + CD25+ FOXP3 + Tregs play an important role in promoting tumor growth. Tregs inhibit activation of both CD4+ and CD8+ T cells, which may serve to suppress anticancer cell immunity (Littman and Rudensky, 2010). Furthermore, T-helper 17 (Th17) could antagonize and counter tumor-suppressive IFN-γ producing CD4 + Th1 cells (Lin et al., 2007).

DCs are a heterogeneous population of innate immune cells that are believed to be among the first cells migrating to the tumor site through VEGF, HGF, β-defensin, CXCL12, and CXCL8 release by cancer and stroma cells (Shurin et al., 2006). They regulate inflammation and constitute an important link between innate and adaptive immunity (Pan et al., 2008). MDSCs are immune cells with two distinct monocytic and granulocytic subsets (Murdoch et al., 2008). They coordinate tumor progression and coordinate angiogenesis through releasing MMP-9 and VEGF, and they promote immune evasion by suppressing antitumor cytotoxic T lymphocytes (CTLs) and NK cells (Talmadge et al., 2007). NK cells are a type of cytotoxic lymphocyte critical to the innate immune system. They are also engaged in reciprocal interactions with DCs, TAMs, T cells and endothelial cells. TAMs represent as much as 50% of the tumor mass (Lewis et al., 2007). These highly flexible multifunctional cells are characterized by plasticity and secretion of numerous immune/inflammatory modulatory cytokines. Most commonly activated macrophages are classified as M1 or M2 cells (Qian and Pollard, 2010). M1s are involved in response of Th1 cells to pathogens and are characterized by high capacity to present antigen, production of proinflammatory cytokines (IL-1, IL-12, TNFα, IFN-γ), and generation of ROS and nitric oxide (NO) with ability to kill pathogens and cells. By contrast, M2s express an immunosuppressive phenotype initializing Th2-type responses through production of IL-10 and inhibition of CTLs. Moreover, M2s promote angiogenesis, ECM remodeling, and repair. In the TME, TAMs have generally an M2-skewed phenotype.

During tumor progression, preinvasive microenvironment with antitumor properties comprises predominantly Th1 and M1 subpopulations with production of IL-12, IFN-γ, and inducible nitric oxide synthase (NOS). The recruitment of monocytes to the tumor is mainly driven by CCL2, a chemokine produced principally by CAFs, while macrophages differentiation and growth are regulated by several GFs, including CSF-1 and GMCSF (Mukhtar et al., 2011). Transition to invasive carcinomas is
marked by establishment of a protumoral microenvironment with a shift from Th1 to Th2 and from M1 to M2, decrease of IFN-γ, and increase of IL-1, IL-6, indoleamine 2,3-dioxygenase, and VEGF. Topographically, immune cells are not randomly located within tumors. Th1 and cytotoxic memory T cells are found at invasive margins and in the core of tumors. NK cells are dispersed within the stroma and at invasive margins. Immature DCs are located in the tumor core, whereas mature DCs infiltrate T cell zones, where they are in close contact with CD4+ and CD8+ T cells. Follicular DCs, TAMs, and follicular helper T cells are in contact with B lymphocytes within B cell zones. B cells are located in tertiary lymphoid structures and at the invasive margins (Goc et al., 2013).

A recent study investigated the potential synergism between cancer cells and TAMs in triple-negative breast cancer treated with adjuvant chemotherapy. Interestingly, the EMT-related kinase AXL showed the highest correlation with the frequency of CD163(+) macrophages. In vitro analysis demonstrated that AXL-expressing cancer cells were able to polarize macrophages toward an M2-like phenotype and modulate a specific pattern of protumor cytokines and chemokines. Selective AXL inhibition impaired the activity of M2-like macrophages, reducing breast cancer cell invasiveness and restoring the sensitivity of cancer cells to chemotherapy. These findings suggest that AXL overexpression in breast cancer cells has prognostic significance and contributes to the functional skewing of macrophage functions. Thus, targeting a kinase involved in cancer progression could help block the cross talk between cancer cells and tumor-promoting immune cells (Bottai et al., 2016).

**Reciprocal interactions between miRNAs and inflammatory/immune cells.** Interactions between miRNAs and inflammatory and immune cells influence cancer cells’ immune escape. Recent study has demonstrated the role of miRNAs in cross talk communication between cancer cells and TAMs. Cancer cells were shown to secrete miR-21 and miR-29a in exosomes. Then, these two miRNAs are taken up by surrounding TAMs and bind to toll-like receptor 8 (TLR8) located inside TAM endosomes, which consequently induce an activation of NF-κB and the secretion of proinflammatory cytokines TNF-α and IL-6 (Fabbri et al., 2012). Implications of this mechanism were extended to the resistance to chemotherapy in neuroblastoma and breast cancer, and as a diagnostic and prognostic biomarker in colorectal cancer (Wang et al., 2015a; Toiyama et al., 2013; Jiang et al. 2010b). Recent data indicate a role of exosomal miR-21 and miR-155 in the cross talk between cancer cells and TAMs in the resistance to chemotherapy through a novel exosomal miR-21/TLR8-NF-κB/exosomic miR-155/TERF1 signaling pathway. In neuroblastoma, miR-155 doesn’t derive from cancer cells but from TME and is secreted by the exosome back to the cancer cell, where it silences TERF1 gene. When miR-155 is delivered via the exosomes, it suppresses TERF1, leading to increased telomerase activity and increased resistance to chemotherapy (Challagundla et al., 2015; Iorio et al., 2005). In a similar mechanism of interaction, M2 TAM-derived exosomes containing miR-223 are delivered to breast cancer cells and promote invasiveness via the Mef2c-β-catenin pathway (Yang et al., 2011). Additionally, TAMs secrete CCL18, which reduces miR-98 and miR-27b expression via the Ras/ERK/P38/akt/NFκB/Lin28b signaling pathway in cancer cells that consequently enhances EMT and metastasis of breast cancer cells (Lin et al., 2015). Furthermore, miRNAs have been shown to directly influence the number of infiltrating TAMs. MiR-92a suppression affects the number of infiltrating TAMs in breast cancer, miR-142-3p down-regulation protects tumor-promoting M2-phenotype TAMs against apoptosis in glioblastoma, and both were correlated with overall survival (Nilsson et al., 2012; Xu et al., 2014). Similarly, IL-6 released from tumor cells induces miR-17 and miR-20a down-regulation in TAMs, which induces HIF-2α and transcription of proangiogenic genes (Xu et al., 2013). In breast cancer models, TAMs with suppression of miR-146a and miR-222 demonstrate promotion of M2-type polarization and macrophage chemotaxis, respectively (Li et al., 2015b). Furthermore, miR-125b has been shown to promote TAM activation by increased T cell activation as well as increased sensitivity to IFN-γ, which slows tumor growth. MiR-125b is upregulated in certain leukemias and down-regulated in many solid cancers (Chaudhuri et al., 2011). Similarly, miR-23a/27a/24-2 cluster regulates M1 and M2 polarization through a negative feedback loop (Ma et al., 2016). This miRNA cluster has been shown to be down-regulated in the TAMs of breast cancer patients, thereby promoting tumor cell growth (Ma et al., 2016). Alternatively, miR-511-3p tunes down the protumoral MRC1(+) TAMs gene signature and inhibited tumor growth (Squadrito et al., 2012). Functional study indicates that expression of miR let-7d significantly inhibited renal cell carcinoma (RCC) cell proliferation, migration, and peripheral blood monocyte recruitment in vitro, as well as tumor growth, metastasis, and TAMs in vivo (Su et al., 2014). Otherwise, miRNAs function to shift the local inflammatory TME to be immunosuppressive and immune tolerant, allowing cancer cells to grow and metastasize and escaping immune surveillance. Tumor-derived TGFβ induces miR-183 in NK cells, thereby suppressing DAP12 transcription, a necessary protein in NK-mediated tumor cell death (Donatelli et al., 2014). In hepatocellular carcinoma (HCC), miR-146a overexpression suppresses antitumor response by NK cells and CTLs through increased inflammatory cytokines and TGFβ, leading to increased cell growth (Sun et al., 2015). Similarly, miR-92a is released from glioma cells and induces NK cell expression of IL-6 and IL-10, significantly attenuating the expression of NK cell-derived antitumor molecules, including perforin, Fas ligand, and IFN-γ (Tang et al., 2014). Furthermore, miR-210 has also been shown to silence PTEN1, HOXA1, and TP53I11 transcription, decreasing the tumor’s susceptibility to CTLs (Noman et al., 2016). Moreover, miR-23a directly targets CD107a expression in NK cells, decreasing the NK cell response (Berchem et al., 2015). Subsequently, increased secretion of miR-214 in microvesicles from various human cancers leads to down-regulated PTEN in the regulatory T cells, promoting Treg expansion and enhanced immunosuppression in the TME (Yin et al., 2014). Most interestingly, miRNA can not only alter inflammatory antitumoral functions, but can change the cell surface ligands on cancer cells to allow for immune evasion from the NK group 2D (NKG2D) receptor. In both breast and ovarian cancer stem cells (CSCs), overexpression of miR-20a has been shown to promote immune evasion from NK cells through decreased transcription of major histocompatibility complex (MHC) class I chain-related protein A and B (MICA and B), the ligand of the NKG2D receptor on NK and CTLs (Wang et al., 2014a; Xie et al., 2014). Similarly, miR-10b directly binds MICB and down-regulates its membrane expression, decreasing...
KNG2D-mediated tumor killing (Tsukerman et al., 2012). In contrast, miR17/20a functions as a tumor suppressor by reprogramming tumor cells for NK cell-mediated cytototoxicity via Mekk2-Mek5-Erk5 pathway (Jiang et al., 2014). Besides, miRNAs can change the expression of KNG2D receptor ligands, inhibiting NK and T cells. For example, miR-34 led to down-regulation of ULBP2, diminishing tumor cell recognition by NK cells (Heinemann et al., 2012). Comparatively, miR-29 control B7-H3 protein expression, which inhibits NK cells and T cells and is implicated in immune escape of cancer cells (Xu et al., 2009).

There is a close mutual interact between cancer cells undergoing EMT and TAMs at the invasive front of tumor. TAMs induce EMT of cancer cells by activating the EMT signaling pathway and ECM remodeling of TME. In addition, TGF-β and tumor necrosis TNF-α are commonly suggested as EMT inducers secreted from TAMs (Son et al., 2017). It has been shown that mesenchymal-like breast cancer cells activate macrophages to a TAM-like phenotype by granulocyte-macrophage colony-stimulating factor (GM-CSF). Recent findings suggest that a positive feedback loop between GM-CSF and CCL18 is important in breast cancer metastasis. In co-culture systems and humanized mice, CCL18 from TAMs induces cancer cell EMT. Moreover, the inhibition of GM-CSF or CCL18 breaks this positive loop and reduces cancer metastasis. High GM-CSF expression in breast cancer is associated with more CCL18(+/-) macrophages, cancer cell EMT, enhanced metastasis, and reduced patient survival (Su et al., 2014). Liu and colleagues hypothesized that M2-polarized TAMs could promote EMT in pancreatic cancer cells partially. They showed that co-culture of pancreatic cancer cells with M2-polarized TAMs decreased the expression of the epithelial marker (E-cadherin); increased up-regulated mesenchymal markers (Vimentin and Snail); and increased proliferation, migration, and MMP-2 and MMP-9 proteolytic activity through TLR4/IL-10 signaling. Application of TLR4 siRNA and neutralizing antibodies against TLR4 and IL-10 markedly inhibited E-cadherin reduction and the up-regulation of Vimentin and Snail. Furthermore, activation of TLR4 signaling by lipopolysaccharide profoundly increased the EMT of pancreatic cancer cells (Liu et al., 2013).

This complex interplay among cancer cells, CAFs, and M2 TAMs cooperates in increasing tumor cell motility, ultimately fostering cancer cells escaping from primary tumor and metastatic spread, as well as in driving de novo angiogenesis (Comito et al., 2014).

Reciprocal regulation between lncRNAs and inflammatory/immune cells. LncRNAs have been recently identified to regulate with inflammatory and immune cells in chronic inflammation and immune pathologies. LncRNA-Cox2 was identified as a dynamically regulated gene induced by TLR ligands that, in turn, acts to both promote and repress inflammatory gene expression (Carpenter et al., 2013). Additionally, lncRNAs, including THRIL, lnce13, and an antisense lncRNA AS-IL-1a also regulate inflammatory gene expression in myeloid cells (Li et al., 2014a; Castellanos-Rubio et al., 2016; Chan et al., 2015). In T cells, lncRNA Rmrp regulates effector functions of Th17 cells (Huang et al., 2015). Recently, long intergenic ncRNA erythroid prosurvival (lincRNA-EPS), also known as Tce3paas1, has been identified as an important transcriptional brake that curbs inflammatory gene expression in macrophages (Atianand et al., 2016). Similarly, lincRNA-Tnfaip3 acts as a coregulator of nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) to modulate inflammatory gene transcription in macrophages (Ma et al., 2016). Recent functional assay revealed an important link between lncRNAs UCA1 and TAMs in breast cancer cells via regulating AKT signaling (Chen et al., 2015).

These data, coupled with the role of CAFs and TAMs in cancer cell EMT, should focus great interest for innovative strategies aimed at the cotargeting of inflammatory cells and fibroblasts to improve therapeutic efficacy.

**ECM stiffness**

ECM is a biopolymer fiber network that generates a mechanically stable support for epithelial cells. ECM is composed of proteins, proteoglycans, and glycosaminoglycans. ECM proteins include various collagens, laminins, and fibronectins (Guo and Giancotti, 2004; Parsons et al., 2010). Collagens are principal proteic components of most ECMs and represent the dominant ECM constituent of mesenchymal tissue (Guo and Giancotti, 2004). Mechanical properties of ECM are dependent on collagen content fiber thickness and the extent of intrafibrillar cross-links, porosity, and mesh size (Shoulders and Raines, 2009). Laminin, an important protein component of ECM, can participate in integrin engagement, specifically in the assembling of basement membrane (Guo and Giancotti, 2004). It is known that the alteration of the constituents of the basement membrane is a hallmark of tumor invasion and progression. Though less abundant than collagens, fibronectin is a crucial protein constituent of the ECM to which integrins can bind (Guo and Giancotti, 2004). Integrins are heterodimeric receptors responsible for anchoring cells to ECM proteins and for signal transduction. Increased rigidity augments release of active TGFβ from ECM-associated LTBP-1 via interaction of integrins αvβ3, αvβ5, αvβ6, and αvβ8 expressed by myofibroblasts (Vannucci, 2015).

Adhesion modulatory proteins like fibulin 1 and tenascin C are important effectors of cell-matrix interactions during tissue remodeling and regeneration. They comprise a diverse group of matricellular proteins that confer anti-adhesive properties to ECM (Williams and Schweizbauer, 2009). Remodeling of the ECM and alterations in cell-cell and cell-ECM interactions are the first barriers that must be overcome for a cancer cell to migrate and travel to distant sites. During tumor progression, ECM composition, and structure change continuously. Increased ECM stiffness plays a role in regulating focal adhesion maturation, cell spreading, actin stress fiber formation, and cell mobility. Thus, ECM stiffness controls motility strategies of cancer cells (Taddei et al., 2013). Interestingly, decreased stiffness of ECM with large mesh sizes allows cancer cells to migrate in an amoeboid fashion, filter through gaps within ECM, and move at relatively high velocities, thus resisting drugs targeting proteases or integrins (Friedl and Wolf, 2010). In contrast, an increased stiffness favors a mesenchymal motility with up-regulation of integrin-mediated contacts and focal adhesions, and enhances the rate of migration by degrading the fibers matrix with MMPs, serine proteases, and cathepsins (Wolf et al., 2007).

Recently, Twist1 has been reported as an essential mechano-mediator that promotes EMT in response to increasing ECM stiffness. High ECM stiffness promotes nuclear translocation of Twist1 by releasing Twist1 from its cytoplasmic binding partner G3BP2. Loss of G3BP2 leads to constitutive Twist1 nuclear localization and synergizes with increasing ECM stiffness to induce
EMT and promote tumor invasion and metastasis. In breast cancer, collagen fiber alignment, a marker of increasing ECM stiffness, and reduced expression of G3BP2 together predict poor survival. Altogether, these findings reveal a Twist1-G3BP2 mechanotransduction pathway that responds to biomechanical signals from the TME to drive EMT, invasion, and metastasis (Wei et al., 2015a).

Reciprocal regulation between miRNAs and ECM. MiRNAs influence cancer cell migration and metastasis by regulating ECM. A recent study points out the relation between circulating miR-21, miR-26, miR-29, miR-30, miR-133a, and ECM fibrosis in heart failure patients (Rubiš et al., 2017). Emerging evidence shows that expression levels of numerous collagen types are also regulated by miRNAs. MiR-29 targets many distinct collagen-encoding mRNAs and plays a crucial role in regulating collagen-dependent ECM homeostasis. MiR-29 is capable of suppressing expression of collagen type I α1, collagen type III α1, collagen types IV α1 and α2, collagen types V α1 and α2, collagen type V α3, collagen type VII α1, and collagen type VIII α1 (Liu et al., 2012; van Rooij et al., 2008). In HCC, miRNA let-7g suppresses metastasis partially through targeting collagen type I α2 (Ji et al., 2010). In addition to regulating the expression of various collagens, miR-29 is also capable of down-regulating levels of laminin γ1 (Sengupta et al., 2008). Laminin γ1 and integrin β1 are also identified as endogenous targets of miR-124 (Cao et al., 2007). Similarly, fibronectin expression can be regulated by miRNAs like miR-17 and miR-199a (Shan et al., 2009; Lee et al., 2009). In contrast, the anti-adhesive molecule tenasin C is a downstream target of miR-335. In breast cancer, miR-335 has been shown to suppress metastasis and migration through targeting of ECM component tenasin C (Tavazoie et al., 2008). Furthermore, recent data demonstrated that ECM stiffness can engage a specific molecular pathway, miR-18a regulation of PTEN and homeobox A9 (HOX9), which could be clinically exploited. It has been shown that increased ECM stiffness induces miR-18a to reduce levels of PTEN by decreasing levels of HOX9. In breast cancer, ECM stiffness was correlated directly and significantly with miR-18a expression. Additionally, miR-18a expression was highest in basal-like breast cancers in which PTEN and HOX9 levels were lowest and predicted for poor prognosis in luminal breast cancers (Mouw et al., 2014).

When assessed together, the above-cited data revealed that several miRNAs are capable of regulating downstream effector molecules or signal transduction associated with multiple cell programs involved in controlling cell-cell adhesion, cytoskeletal regulatory proteins, cell-matrix adhesion molecules, and ECM proteins.

Reciprocal regulation between miRNAs and MMPs. MiRNAs have been found to regulate MMPs’ actions. In HCC, MMP-2 and MMP-9 expression is up-regulated by miR-21 via PTEN pathway down-regulation (Meng et al., 2007). Similarly, reduced levels of miR-138 in cholangiocarcinoma induced up-regulation of RhoC, leading to increased levels of MMP-2 and MMP-9 (Wang et al., 2013). Conversely, in breast cancer, loss of miR-29b expression causes increased MMP-2 and MMP-9, which suggests that miR-29b suppresses MMP-2 and MMP-9 (Chou et al., 2013). In ovarian cancer, placental growth factor (PLGF) suppresses miR-543, which inhibits MMP-7 translation, and enhances cancer cell invasion through MAPK-p38-dependent activation of Zeb2. Therefore, high levels of PLGF as seen in ovarian cancer increase MMP-7 levels and, thus, the cancer’s invasion ability (Song et al., 2015; Song et al., 2016). In a previous study, we revealed that EGFR was markedly underexpressed in breast carcinoma (Meseure et al., 2012). In comparison, patients with EGFR up-regulation have a less favorable prognosis than those with EGFR-negative breast cancer (Koletsa et al., 2010). A recent study showed that miR-24 can activate EGFR phosphorylation in breast cancer. Authors demonstrated that MMP-2 and MMP-11 are up-regulated due to miR-24 modulation of the EGFR pathway (Du et al., 2013). It seems that elevated levels of miR-21 down-regulate the tissue inhibitor of metalloproteinases-3 (TIMP-3) in gliomas and TIMP-2 in breast cancer, enhancing tumor local invasion and metastasis (Du et al., 2013; Gabriely et al., 2008). In addition, several miRNAs have been found to target integrins, including miR-93, which promote tumor growth and angiogenesis by suppressing integrin-β8 expression (Fang et al., 2011). Accordingly, miR-183, miR-124, and miR-29b suppress integrin-β1, and miR-29b suppress integrin-α6 (Hunt et al., 2011; Li et al., 2010).

Finally, miRNAs directly affect expression of many stromal components. Overexpression of miR-17 results in decreased cell adhesion, migration, and proliferation by repressing expression of both fibronectin and fibronectin type-III domain containing 3A (FNDC3A) (Shan et al., 2009). In HCC, miRNA let-7g level is inversely correlated with type 1 collagen α2 level, let-7g may suppress metastasis partially through targeting this collagen, and low miR let-7g levels are directly correlated with poor survival (Ji et al., 2010). Similarly, decreased let-7d level in RCC is associated with advanced tumor stage and increased vascular invasion by enhancing secondary collagen type III α1 and CCL7 expression (Su et al., 2014).

Reciprocal regulation between lncRNAs and ECM. A subset of lncRNAs is tightly linked to collagen genes and numerous proteins that regulate ECM during formation of fibrosis in liver, pulmonary, and skin diseases. Many of these lncRNAs are regulated by TGFβ and form networks with genes encoding key components of ECM (Zhou et al., 2016a; Wang et al., 2016). In lung cancer, tumor-promoting collagen type 1 up-regulates expression of HOTAIR. A three-dimension organotypic culture mode suggests that collagen type 1 transcriptionally activates expression of HOTAIR in cancer cells (Zhuang et al., 2013).

Angiogenesis

Blood vessels are composed of perivascular cells termed pericytes, endothelial cells that form the inner lining of the vessel wall and vascular smooth muscle cells. De novo angiogenesis are crucial adaptive events for tumor growth beyond 1–2 mm³ and involve several cellular events including proliferation, migration, vascular transdifferentiation (vascular mimicry), and ECM degradation (Hillen et al., 2007). Angiogenesis results from a balance between activating and inhibitory factors and affects both growth of malignant cells locally and survival at distant sites. Angiogenesis is also induced by CAFs via production of chemokines (CXCL8, CXCL12), MMP-1, MMP-3, MMP-7, MMP-9, MMP-13, MMP-14, VEGF, and COX2 (Shree et al., 2011). Moreover, MDSCs secrete pro-angiogenic chemokines by stimulating ERK1/2 signaling pathway (Chen et al., 2011).
Reciprocal interactions between miRNAs and angiogenesis. Most miRNAs derived from cancer cells have oncogenic activity by promoting angiogenesis and tumor growth and survival (Frediani and Fabbrì, 2016). The miR-17-92 cluster (encoding; miR-17, -18a, -19a, -19b, -20a, and -92a) located on human chromosome 13 was initially described as an oncomiR and was later demonstrated to regulate angiogenesis during normal development and under diseases (Umèzu et al., 2013; Yang et al., 2017). Up-regulation of miR-17-92 was initially found in several lymphoma cell lines and has further been confirmed in different solid tumors (Umèzu et al., 2013; Zhu et al., 2016). The miR-17-92 cluster is directly activated by Myc and modulates a variety of downstream transcription factors that are important in cell cycle regulation and apoptosis, including activation of E2F family and cyclin-dependent kinase inhibitor (CDKN1A) and down-regulation of Bcl2L11/BIM and p21 (Umèzu et al., 2013). Moreover, the miR-17-92 cluster also down-regulates important anti-angiogenic proteins, including thrombospondin-1 (Tsp1) and connective tissue growth factor (CTGF) (Umèzu et al., 2013). Recent analysis revealed that higher expression of miR-17-92 cluster and lower expression of mi-134 and alterations of target gene expression may be associated with the drug-resistant nature of some ovarian cancers (Zhu et al., 2016). Certainly, miRNAs, which are often packaged in tumor cell–derived exosomes, contribute to regulation and balance of pro-angiogenic and anti-angiogenic factors (Frediani and Fabbrì, 2016). Microvesicles from colorectal cancer cells contain miR-1246 and TGFβ3, which are transferred to endothelial cells and are considered to be responsible for pro-angiogenic function by activating Smad 1/5/8 signaling (Yamada et al., 2014). Likewise, exosomal miR-135b from multiple myeloma cells is up-regulated under hypoxic conditions and directly suppresses its target factor–inhibiting hypoxia-inducible factor 1 (HIF-1) in endothelial cells, thus increasing angiogenesis (Umèzu et al., 2014). Comparatively, lung cancer cell line–derived microvesicles contain miR-494, which promotes angiogenesis, in response to hypoxia, mediated by targeting PTEN in endothelial cells through activation of Akt/eNOS pathway (Mao et al., 2015). In breast carcinoma, miR-9–mediated E-cadherin down-regulation results in activation of β-catenin signaling, which contributes to up-regulated expression of the gene encoding VEGF; this leads in turn to increased tumor angiogenesis (Ma et al., 2007; Ma et al., 2010). In addition, tumor-secreted miR-9 promotes endothelial cell migration and angiogenesis by activating the JAK-STAT pathway (Zhuang et al., 2012). Up-regulation of miR-20b and miR-130, as well as miR-497 suppression, regulates VEGF through hypoxia-inducible factor 1α (HIF-1α), supporting increased angiogenesis (Lei Z et al., 2009; Saito et al., 2011; Yan et al., 2015). Similarly, miR-146a suppression, as often seen in HCC, leads to increased VEGF expression through down-regulation of adenomatous polyposis coli (APC) and up-regulation of HAb18G, thereby portending a poor prognosis (Zhang et al., 2015b). Two further miRNAs promoting angiogenesis are similarly induced by the hypoxic TME. The first, miR-210, is an important mediator of the endothelial cell response to low oxygen tension, down-regulating normoxic genes and activating MYC to stimulate cell cycle progression (Zhang et al., 2009b). Studies on various primary tumors types have shown that elevated circulating miR-210 levels are both a potential diagnostic tool as well as a poor prognostic indicator at diagnosis (Ho et al., 2010; Camps et al., 2008). Similarly, hypoxia induces miR-424 expression in endothelial cells, which targets cullin 2 (CUL2), a scaffolding protein essential to the ubiquitin ligase system, thus increasing HIF-α levels (Ghosh et al., 2010). In contrast, a recent study revealed that miRNAs can be transferred to the cancer cells from the endothelium. In breast cancer, miR-503 is released in endothelial exosomes, and upon uptake by cancer cells, limits tumor growth and invasion via inhibition of cyclins CCND2 and CCND1 (Pecot et al., 2013). With enhanced delivery of miR-200 into the tumor endothelium of multiple cancer models, including ovarian, lung, renal, and basal-like breast cancers, a significant reduction in metastasis formation and angiogenesis was noticed (Pecot et al., 2013). MiR-98 down-regulates activin receptor–like kinase-4 (ALK4) and MMP11 expression in breast cancer, which inhibits cell growth and angiogenesis (Siragam et al., 2012). Additionally, miR-126 regulates endothelial cell recruitment and vessel formation through inhibition of insulin-like growth factor binding protein 2 (IGFBP2) and c-Mer tyrosine kinase (MERTK) signaling (Png et al., 2011). Low expression of miR-126 has been correlated to increased microvessel density and worse disease prognosis in multiple cancer types including non-small cell lung cancer, glioblastoma, breast cancer, and gastric cancer (Jusufović et al., 2012). MiR-542–3p has been found to inhibit translation of Angiopoietin-2 mRNA, a potent hypoxia–induced regulator of endothelial cell proliferation and migration (He et al., 2014). Elevated levels of miR-542–3p cause attenuated endothelial cell angiogenesis in culture and reduced tumor burden in mouse models (He et al., 2014). Clinical prognosis in patients with stage III/IV breast carcinoma is inversely correlated with miR-542–3p levels (He et al., 2014). Additionally, miR-210 enlists monocytes and encourages angiogenesis (Taddei et al., 2014). In contrast, microRNA miR-93 promotes tumor growth and angiogenesis by targeting integrin-β8 (Fang et al., 2011). Finally, whereas low miR-126 expression has been shown to correlate with poor metastasis–free survival in breast cancer as noted previously, low miR-126 expression has also been shown to cause increased angiogenesis (Zhang et al., 2013b).

Reciprocal interactions between lncRNAs and angiogenesis. LncRNAs also play important roles in angiogenesis. Microvascular invasion in hepatocellular carcinoma (MVH) is an lncRNA located in the intron of the RPS24 gene encoding a protein that belongs to the S24E family of ribosomal proteins. MVH is associated with angiogenesis, metastasis, and poor recurrence–free survival in HCC. MVH promotes cell growth and inhibits cell apoptosis of HCC via inhibiting miR-199a expression, additional evidence that IncRNA may regulate miRNA expression by modulating target genes of miRNAs at the post-transcriptional level (Shi et al., 2015b). In addition, up-regulated MVH expression promotes cell proliferation and cell cycle and inhibits cell apoptosis in breast carcinoma (Lei et al., 2016). Comparatively, previous data showed that methylation–dependent tissue–specific regulation of the IncRNA MEG3 by miR-29a may contribute to HCC growth and highlight the inter–relationship between miRNAs and lncRNAs, as well as epigenetic regulation of gene expression (Braconi et al., 2011). LncRNA MEG3-knockout mouse showed increased expression of VEGF pathway genes and increased cortical microvessel density (Kumar and Goyal, 2017).
Hypoxia

Hypoxia is a common feature of many tumors. TME is usually under hypoxia because of aberrant new-generating blood vessels and poor blood flow. HIF-1α is considered the master regulator of hypoxia as it regulates proliferation, metabolism, angiogenesis, and metastasis. Classically, cancer cells adapt to hypoxic microenvironment via a metabolism shift from tricarboxylic acid cycle to glycolysis and modification of the pH concentration.

MiRNAs involved in hypoxia-induced EMT. Some miRNAs have been reported to be involved in hypoxia-induced EMT. MiR-130 family has been shown to target DDX6 mRNA, which is a component of the P-bodies and facilitates translation of HIF-1α during hypoxia (Saito et al., 2011). Expression of miR-205 and miR-124, which regulate EMT by targeting Zeb1/2 and MMP-2, respectively, is suppressed by hypoxia (Zell et al., 2013; White et al., 2012). Hypoxia also down-regulates the expression of miR-34a, which acts as a suppressor of Snail and Zeb1. Furthermore, hypoxia decreases miR-34a expression, which promotes EMT in renal tubular epithelial cells by directly targeting Notch1 and Jagged1, and subsequently, Notch downstream signaling (Du et al., 2012).

Reciprocal regulation between lncRNAs and hypoxia. Accumulating evidence suggests that hypoxia-regulated lncRNAs are implicated in cancer reprogramming. Hypoxia modulates lncRNAs expression, including NEAT1, lincRNA-p21, UCA1, HINCUT-1, H19, and ENFA3 by activating their transcription or by inducing epigenetic alterations (lncRNA-LET, WT1 lncRNA) (Choudhry et al., 2014; Gomez-Maldonado et al., 2015). Conversely, hypoxia-induced lncRNAs regulate gene expression through epigenetic changes (WT1 lncRNA, AK058003), by functioning as endogonic competitors (lincRNA ROR, ENFA3), or by interacting with binding protein (lncRNA-LET, lincRNA-p21). Furthermore, hypoxia-induced lncRNAs are associated with cancer cells reprogramming, plasticity, migration, and metastasis using different mechanisms: NEAT1, UCA1, and HINCUTs promote cell survival and proliferation; H19 and UCA1 influence tumor growth via interfering with apoptosis through p53 or Bcl-2 pathway; lincRNA-p21 promotes glycolysis via HIF-1α, which regulates expression of Glut1 and LDHA; MALAT1, ANRIL, and Linc-ROR regulate angiogenesis; and H19, ENFA3, UCA1, and lncRNA-LET are implicated directly in plasticity, invasion and metastasis (Chang et al., 2016; Dong et al., 2016). The positive regulation of H19 lncRNA by HIF-1α may explain its overexpression in metastases (Matouk et al., 2010). In mouse model, H19 is concomitantly induced by both TGFβ and hypoxia, which regulates E-cadherin expression and stimulates breast cancer metastasis through a positive feedback loop between Slug and H19/miR-675 (Matouk et al., 2010). The Linc regulator of reprogramming lncRNA (Linc-RoR) is a hypoxia-responsive that modulates expression of miR-145 and HIF-1α and acts through a hypoxia/miR-145/HIF-1α signaling axis to modulate EMT in vitro and in vivo (Takahashi et al., 2014).

In addition to the above-cited data, hypoxia and HIF-1α can regulate EMT at multiple fronts, including the expression of EMT TFs, EMT-associated pathways, and cytokine (Xu et al., 2016a).

Reactive oxygen species

ROS are produced by cancer and stromal cells and induce a pro-oxidant microenvironment through diffusion of ROS compound H₂O₂. In TME, ROS modulate several factors and signaling pathways including HIF, CXCL12, PDGFβR, TGFβ, and caveolin, which drive onset of inflammation and promote fibroblast-to-myofibroblast transition (Liu et al., 2006). In CAFs, ROS levels increase ECM remodeling, modulate tumor cells metabolism, and activate invasion, angiogenesis, and metastasis (Storz et al., 2005). In contrast, high levels of ROS in cancer cells result from increased metabolism, cytokines, and GFs secretion by stromal cells, mitochondrial DNA mutations, hypoxia, and reduction of antioxidant defenses (Costa et al., 2014). ROS are also implicated in cancer cell proliferation, metabolic reprogramming, genomic instability, plasticity, stemness, escape from immune system, and therapeutic resistance (Erez et al., 2010).

Reciprocal interactions between miRNAs and ROS. Multiple interactions between miRNAs and ROS have been described in cancerogenesis. MiR-210 induces ROS generation under hypoxic condition, leading to a poor prognosis in colorectal cancer (Tagscherer et al., 2016; Chen et al., 2010). MiR-34a inhibits ROS synthesis by silencing genes that code for mitochondrial complexes and other ROS-producing enzymes, contributing to apoptosis resistance (He and Jiang, 2016; Lin et al., 2017). Overexpressed miR-141 and miR-200a modulate oxidative stress by targeting p38α and potentiate tumor growth (Cufí et al., 2012). Conversely, ROS regulate miRNA expression through miRNA biogenesis, transcription factors, and epigenetic alterations. Exogenous H₂O₂ exposure leads to up-regulation of miR-21 while lowering expressions of miR-27a, miR-27b, miR-29b, and miR-328 (He and Jiang, 2016). It is suggested that one of the potential mechanisms utilized by miR-21 to promote tumorigenesis is through alteration of cellular ROS levels. In colorectal carcinogenesis, miR-21 plays an essential role in many aspects, as its up-regulation has been found in tumor tissues, serum, and stool of patients with colorectal cancer (Lin et al., 2017).

Key Regulators of EMT

EMT program is defined as a set of multiple and dynamic transi-sonal states between epithelial and mesenchymal phenotypes, as opposed to a process involving a single binary decision (Nieto et al., 2016). EMT process is highly contextual and sophisticatedly driven by genetic and epigenetic mechanisms and microenvironmental factors.

Key regulators of EMT could be subdivided into three major key players: EMT inducers, EMT core regulators, and EMT effectors. EMT-inducing signals require cooperation between multiple signaling pathways including Wnt, Notch, Hedgehog (Hh), and GF receptor signaling cascades such as transforming growth factor-β (TGFβ), FGF, EGF, and VEGF (Xu et al., 2016b). The majority of EMT pathways converge on the level of EMT-associated transcription factors (EMT-TFs). The TFs Snail (zinc finger proteins Snail1, Snail2, and Slug), Zeb (zinc finger and homeodomain proteins Zeb1 and Zeb2), and Twist (basic helix-loop-helix proteins Twist1, Twist2, E12, E47, and Id), and the newly discovered Prrx1 (paired-related homeobox transcription factor 1), play a central role during oncogenic EMT (Cao et al., 2017; Diepenburk, 2016). EMT effectors usually are proteins, which determine epithelial or mesenchymal identity of a cell, such as E-cadherin, α-catennin, γ-catennin, and Vimentin, or promote cell migration and invasion during EMT, like fibronectin.
**EMT inducers**

EMT-inducing signals require cooperation between multiple factors and signaling pathways. In addition to the complex network of signaling pathways, miRNAs and lncRNAs are being evolved as a new player in the induction of EMT (Garg, 2015). Many growth factors, such as TGFβ, FGF, EGF, and VEGF, and their associated signaling proteins, such as NF-κB, ERK, PI3K/AKT, Hh, Notch, and Wnt, are engaged to trigger and complete an EMT process (Xu et al., 2016).

**TGFβ signaling pathway.** TGFβ is a well-known EMT initiator and has a predominant role in promoting metastasis in many tumor cells through tightly controlling the EMT process. TGFβ activates Smads by binding to serine threonine kinase receptors type I and type II (TβRI and TβRII). TβRI is phosphorylated by TβRII and then activates Smads. Activated Smads translocate into the nucleus to interact with various EMT-TFs and transcriptional co-activators and regulate the transcription of target genes. TGFβ activates expression of Snail via Smads pathways as downstream effectors to repress expression of E-cadherin and claudin. In addition to canonical TGFβ/Smad pathway, TGFβ has been shown to regulate expression of EMT markers through Smad-independent (non-canonical) TGFβ signaling pathways (Zhang, 2009a).

Moreover, PI3K/AKT and p38-MAPK, as well as induction of miRNAs and lncRNAs, have been reported to have important roles in TGFβ-induced EMT (Xu et al., 2016a; Garg, 2015). Treatment of mammalian epithelial cells with TGFβ-induced miR-155, whose knockdown suppressed TGFβ-induced EMT, migration, and invasion through direct targeting of RhoA (Kong et al., 2008).

LncRNA activated by TGFβ (Lnc-ATB), can mediate TGFβ-induced EMT and has been shown to promote metastasis in HCC, gastric, colorectal, and breast cancers (Yuan et al., 2014; Saito et al., 2015; Iguchi et al., 2015; Shi et al., 2015a). In addition, MALAT1 is associated with the suppression of SUZ12, which prevents the ability of Snail1 from down-regulating E-cadherin. Thus, the induction of MALAT1 by TGFβ results in decreased E-cadherin and increased N-cadherin/ fibronectin, leading to enhanced EMT (Fan et al., 2014). Interestingly, TGFβ1 secreted by CAFs induces EMT of urothelial bladder cancer through IncRNA-ZEB2/NAT (Zhuang et al., 2015). LncRNA-HIT (HOTAIR associated transcript induced by TGFβ) is also involved in TGFβ-induced EMT. The effects of lncRNA-HIT on EMT, migration, and invasion in breast cancer were rescued through introduction of ectopic E-cadherin (Richards et al., 2015). These findings suggest that lncRNAs can be induced by TGFβ and play a key role in TGFβ-induced EMT.

**MEK/ERK signaling pathway.** The MEK/ERK pathway is another major pathway through which IncRNAs regulate EMT. It has been demonstrated that overexpression of BANCR (BRAF-activated ncRNA) induces cancer cell migration by inducing EMT via the MEK/ERK signaling pathway, and treatment with the MEK inhibitor affects the expression of epithelial and mesenchymal markers in colorectal cancer cells (Guo et al., 2014). Similarly, MANCN (MALAT2-activated IncRNA) contributes to gastric cancer migration by inducing EMT via a MEK/ERK-dependent mechanism, as the MEK/ERK pathway inhibitor inhibits cancer metastasis (Chen et al., 2015).

**Wnt/β-catenin signaling pathway.** Activation of Wnt/β-catenin signaling pathway has been shown to induce EMT. Wnt couples with its cell surface receptors, the low-density lipoprotein receptor and membrane protein Frizzled, to activate and stabilize β-catenin, which is the central component of the Wnt/β-catenin signaling, moving from the cytoplasm to the nucleus to regulate the transcription of Wnt target genes. In the nucleus, β-catenin acts as a coactivator of T cell factor/lymphoid-enhancing factor-1 (TCF/LEF-1) to promote the transcription of Snail, Slug, and Twist, which in turn represses E-cadherin. Wnt inhibitory factor 1 (WIF-1) plays an important role in the Wnt/β-catenin signal pathway. It has been demonstrated that HOTAIR (HOX transcript antisense intergenic RNA), an EMT-associated lncRNA and a powerful predictor of metastasis, inhibits WIF-1 expression and activates the Wnt pathway in squamous cell carcinoma of esophagus (Ge et al., 2013; Zhou et al., 2014a; Wu et al., 2014). Additionally, HOTAIR can directly decrease WIF-1 expression by promoting its histone H3K27 methylation in the promoter region, and then activates the Wnt/β-catenin signaling pathway (Ge et al., 2013). In addition, MALAT1 promotes EMT by activating Wnt signaling pathway, up-regulating EMT-TFs Zeb1, Zeb2, Snail2, and/or Slug, and down-regulating E-cadherin in bladder and breast cancer cells (Han et al., 2013; Ying et al., 2012; Meseure et al., 2016a). LncRNAs UCA1 and HOTTIP can promote EMT by activating Wnt/β-catenin signaling pathway (Li et al., 2014b; Sang et al., 2016). H19 is associated with EZH2, and this association results in the activation of Wnt/β-catenin and subsequent inhibition of E-cadherin (Luo et al., 2013). Thus, Wnt signaling is an important target of lncRNAs to regulate EMT.

**Hh signaling pathway.** Hh signaling pathway can promote EMT and maintain CSCs. These cells are commonly associated with EMT and subsequent tumor metastasis. Hh signaling is orchestrated by two transmembrane receptors, Patched (Ptc) and Smoothened (Smoo). The Hh family include three homologous Hh ligands: Sonic hedgehog (Shh), Indian hedgehog (Ihh), and Desert hedgehog (Dhh). Hh ligands can activate Ptc, release Smo, and then initiate an intracellular cascade that activates the Gli family of transcription factors. As a marker of the Hh pathway activity, Gli promotes EMT by inducing the transcription of target genes such as Ptc, Wnt, and Snail. In addition, Hh signaling can cooperate with other signaling pathways such as Wnt, Notch, FGF, and TGFβ to modulate EMT-induced CSCs signaling network (Xu et al., 2016a).

LncRNA-Hh impinges upon EMT and enhances CSC-like stemness by modulating the Hh signaling. Specifically, lncRNA-Hh transcriptionally regulated by Twist directly targets GAS1 to stimulate the activation of Hh. The activated Hh increases Gli expression and enhances the expression of Sox2 and Otx4 to maintain CSCs (Zhou et al., 2016b).

Collectively, these findings demonstrate that EMT is regulated by an intricate network of signaling pathways. Several miRNAs and lncRNAs regulate these pathways to induce changes of EMT at various levels. Thus, understanding the cross talk between EMT-inducing signaling pathways and their regulation by miRNAs and lncRNAs can provide fundamental knowledge to the molecular processes of EMT.

**EMT core regulators**

EMT-TFs core regulators comprise four main families: Snail1, Snail2, and slug; Zeb1 and Zeb2; Twist1, Twist2, E12, E47, and Id; and Prx1. During EMT, TFs repress epithelial traits (E-
cadherin, desmplakin, and claudins) and induce expression of a mesenchymal and migrating phenotype (Vimentin, N-cadherin, CD44, β6-integrin, fibronectin, and MMPs). EMT irreversibility involves important epigenetic mechanisms implicating covalent modifications of DNA and histone proteins, as well as dysregulations of ncRNAs. Crucial links have been recently identified between classical EMT-TFs that bind DNA and numerous co-activators and co-repressors implicated in epigenetic regulation of EMT (Li et al., 2013). While several EMT-TFs are implicated in a transient transcriptional repression of Cdh1 gene, a stable epigenetic silencing of E-cadherin is coordinated by histone-modifying enzymes belonging to the two polycomb repressive complexes [PRCs], PRC1 and PRC2, and the histone demethylase lysine-specific demethylase 1A (LSD1). In colorectal cancer, Snail1 is associated with Cdh1 promoter and enables subsequent recruitment of the two chromatin-modifying enzymes EZH2 and SUZ12 belonging to the PRC2 complex to catalyze trimethylation of H3K27 in nearby nucleosomes and to silence Cdh1 gene transcription. Interaction between Snail1 and LSD1 allows silencing of several important epithelial genes (Liu et al., 2013).

Reciprocal regulation between miRNAs and EMT-TFs. MiRNAs are implicated in regulation of EMT through binding to other regions of targeted mRNAs (D’Amato et al., 2013). MiRNAs maintain epithelial phenotypes by post-transcriptionally inhibiting mRNAs that encode EMT-TFs. In contrast, classic EMT-related TFs are transcriptional regulators of miRNAs. During EMT, members of miR200 and miR205 families, which are physiologically implicated in suppression of TGFβ, NF-kB, cell migration, and resistance to anoikis, are frequently repressed by Zeb-TFs (Ying et al., 2012).

Although multiple miRNAs control EMT, two regulatory networks have been described that can be considered as the core regulatory machinery: the miR34-Snail1 and miR200-Zeb1 axes. These two miR-TF axes employ a double-negative feedback mechanism in which miR34-Snail1 and miR200-Zeb1 repress each other. Snail1 and Zeb1 further repress miR200 and miR34, respectively. At this level, other TFs, such as Ovol1/2 and Grhl2, further feed into this core regulatory machinery to protect the epithelial phenotype. The miR34-Snail1 and miR200-Zeb1 core not only contribute to the epigenetic control of EMT but are also targets for epigenetic modifications. Downstream of the miR34-Snail1 and miR200-Zeb1 axes, regulation of transcript processing would shape the landscape of epithelial and mesenchymal effectors, for example, through alternative splicing. These EMT effectors may also be subject to epigenetic modifications. How other TFs, like Twist1 and Prrx1, affect the network and its epigenetic control requires further study, though it is clear that, unlike Snail and Zeb, they are much more potent mesenchymal promoters than epithelial repressors (Nieto et al., 2016). In addition to direct regulation of E-cadherin-encoding mRNA, miRNAs play a crucial role in determining E-cadherin levels through their capacity to modulate expression of the transcription factors Zeb1 and Zeb2, which can repress transcription from the E-cadherin gene (Valastyan and Weinberg, 2011). The miR-200 family, which is composed of five members (miR-141, miR-200a/200b/200c, and miR-429), inhibits translation of Zeb1 via a double-negative feedback loop that prevents EMT by stabilizing epithelial phenotype and E-cadherin expression. In normal epithelial cells, miR-200 family members inhibit Zeb1 expression resulting in E-cadherin synthesis. During EMT, cells lose miR-200, which in turn activates Zeb1 with eventual repression of E-cadherin synthesis (Senfter et al., 2016). Several studies identified the involvement of the miR-200/Zeb axis in the EMT of many cancer types, especially in colorectal carcinoma (Hur et al., 2013; Paterson et al., 2013). More recent data linked the miR-200/Zeb1 axis with cytoskeletal reorganization, as well as matrix-dependent tumor invasion and metastasis. This study revealed that for Zeb1-dependent EMT, an integrin β1-collagen interaction with the ECM is needed to mediate focal adhesion kinase (FAK) signaling, which promotes invasion and metastasis (Ungewiss et al., 2016). Moreover, CRKL, an adaptor molecule belonging to the CRK family, is identified as a direct target to relocate sites of integrin-mediated focal adhesion formation. Consequently, miR-200 modulates focal adhesion formation via the FAK/Src complex assembly, resulting in cytoskeletal reorganization. CRKL expression is negatively regulated with the miR-200 family and positively associated with Zeb1 and Src signaling, leading to poor outcomes for patients with high CRKL levels in different tumor types (Ungewiss et al., 2016). Interestingly, lysyl oxidase-like 2 (LOXL2), a principal isoform that cross-links and stabilizes insoluble collagen deposition in tumor, is directly regulated by the same miR-200/Zeb1 axis. This novel mechanism driving tumor metastasis delineates collagen as a prognostic marker in tumor progression (Peng et al., 2017). All these findings highlight the critical ECM-tumor cell interactions regulated by miR-200/Zeb1-dependent EMT that activate intracellular signaling pathways responsible for tumor cell invasion and metastasis. A recent molecular analysis revealed that the EMT transcription factor grainyhead-like 2 (Grhl2) regulate epithelial differentiation by directly modulating expression of the adherens junction gene Cdh1 and the tight junction gene Cldn4 (claudin 4) (Werth et al., 2010; Werner et al., 2013). In cancer cells, Grhl2 acts as pivotal gatekeeper for EMT via the miR-200/Zeb1 axis. A down-regulation of Grhl2 increases the levels of histone mark H3K27me3 promoters and Grohl2-binding sites at miR-200b/a and E-cadherin genes, which results in increased cell migration, invasion, and motility (Chung et al., 2016). The miR-200 family is overexpressed in many solid tumor cell lines, particularly breast cancer, and is secreted into extracellular vesicles to act as an important regulator of the EMT (Le et al., 2014). Moreover, Twist1 and Zeb1, respectively, activate transcription of two prometastatic miRNAs: miR10b and miR21. Similarly, miR-409-3p/5p overexpression has also been shown in prostate cancer to induce the EMT, promote cell growth, and repress tumor suppressors, notably RSU1 and STAG2 (Josson et al., 2015).

It has been shown that overexpression of miR-302a resulted in evident decreases in the expressions of Snail, Slug, Zeb1, and Zeb2. Moreover, miR-302a overexpression was shown to inhibit proliferation and invasion of colorectal cancer cells by reducing the expressions of related proteins through suppressing the MAPK and PI3K/Akt signaling pathways. These results indicate that overexpressing miR-302a suppressed EMT through down-regulation of TFs, thereby inhibiting cancer cell invasion and metastasis (Wei et al., 2015b).

**EMT effectors**

EMT can be considered as a continuum, whereby cells exhibit epithelial, intermediate, and mesenchymal phenotypes. During this transition, epithelial cells sequentially lose apico-basal polarity and cell-cell adhesions and gain front-back polarity and
enhanced cell matrix interactions (Nieto et al., 2016). Cadherin-mediated cell-cell adhesion is a highly dynamic process enabling reorganization of cancer cells during EMT. Accordingly, loss of cell-cell adhesion in cancer cells during EMT is correlated with down-regulation of E-cadherin as well as increased tumor cell proliferation and invasiveness.

**MiRNAs and lncRNAs involved in the regulation of EMT effectors.** As mentioned earlier, miRNAs regulate E-cadherin-encoding mRNA and play a crucial role in determining E-cadherin levels through their capacity to modulate expression of Zeb1 and Zeb2, which can repress transcription from the E-cadherin gene (Fig. 1) (Valastyan, 2012).

lncRNAs regulate plasticity through directly or indirectly modulating EMT markers (Xu et al., 2016a). Depletion of HOTAIIR increases E-cadherin expression while concomitantly decreasing expression of Vimentin (Wu et al., 2014). Additionally, HOTAIIR and miR-10b have been shown to promote malignant transformation of normal liver stem cells through down-regulation of E-cadherin and induction of EMT (Ye et al., 2015). In HCC, lncRNA-Dreh regulates tumor growth and metastasis by combining with Vimentin and repressing its expression (Huang et al., 2013a). Accordingly, lncRNA AOC4P exerts a tumor-suppressive effect on EMT and tumor progression in HCC by binding to Vimentin and enhancing Vimentin degradation (Wang et al., 2015b). Comparatively, lnc00152 knockdown suppresses EMT program in gastric cancer by decreasing N-cadherin and Vimentin and increasing E-cadherin expression (Zhao et al., 2015). In contrast, overexpression of BANCR in lung cancer modulates EMT through regulation of E-cadherin, N-cadherin, and Vimentin expression (Sun et al., 2014). Based on experimental results, SPRY4 intronic transcript 1 (SPRY4-IT1) plays an important role in cell growth, migration, and EMT of glioma cells by down-regulating expression of E-cadherin and increasing expression of fibronectin and Vimentin. Down-regulation of SPRY4-IT1 blocks the EMT process (Liu et al., 2015). lncRNA-activated by TGFβ (lncRNA-ATB) promotes invasion-metastasis cascade in HCC and colorectal cancer via down-regulation of E-cadherin and promotion of EMT process. Reduction of lncRNA-ATB increases expression of epithelial markers E-cadherin andZO-1, decreases expression of mesenchymal markers Zeb1 and N-cadherin, and significantly influences colon cancer cell progression (Yuan et al., 2014).

**EMT and cancer stem cells**

CSCs are commonly associated with EMT and subsequent tumor metastasis. CSCs and epithelial mesenchymal plasticity paradigms...
share striking parallels, as EMT gives rise to cells with stem-like properties, and CSCs exhibit an EMT gene expression profile. Accordingly, CSCs probably represent a highly dynamic cell population, continuously differentiating between epithelial and mesenchymal status (Hatina and Schulz, 2012). The physiologic stem cell niche normally orchestrates balance between self-renewal, cell proliferation, and differentiation. Conversely, a dysregulated CSC niche allows CSCs to initiate a complex epigenetic reprogramming during tumor progression with generation of heterogeneous subpopulations of tumorigenic CSCs and more differentiated non-tumorigenic cells (Yasuda et al., 2010). The TME could play crucial roles via hypoxia in maintenance of CSCs properties, quiescence, activation of CSC-associated pathways, and cell motility (Chang et al., 2013). The origin of CSCs from normal embryonic or adult stem cells, more mature progenitors, or differentiated epithelial cancer cells is still unresolved (May et al., 2011). Recent data have revealed that their epigenetic landscape is evocative of an embryonic rather than an adult stem origin, with expression of Dnmt1 and HDAC1 rather than MLL family of histone methyltransferases. They exhibit dynamic epigenetic profiles enriched in euchromatin with low levels of DNA methylation, absence of bivalent mark H3K4me3/H3K27me3, high levels of activation mark H3K4me3, and repressive histone mark H3K27me3 at tumor suppressor genes. CSC regulation is driven by key regulatory and morphogenetic pathways (Wnt, Notch, Bmp, Shh) through direct cell-cell contact (endothelial cells via Notch pathway in glioblastoma) or secreted signaling components (HGF) provided by stromal cells of the CSC niche (Reya and Clevers, 2005). CSCs can be isolated based on their growth properties or by sorting using cell surface antigens, metabolic markers such as CD44, CD24 and CD133, and activity of aldehyde dehydrogenase 1 (ALDH1). Numerous biomarkers have been identified and render identity of CSCs a matter of debate (Vermeulen et al., 2010). Expression of these biomarkers is regulated by DNA methylation and histone modifications controlled by chromatin-modifying enzymes, miRNAs and lncRNAs. CSCs typically resist cancer therapies by having an up-regulated abundance of DNA repair enzymes, lower levels of ROS, and dormant or slow-cycling properties (Vincent and Van Seuningen, 2012).

Many studies have recently linked the CSC phenotype to cancer cells undergoing EMT (Zaravinos, 2014). In mouse model, EMT promotes the metastasis of prostatic cancer cells with CSC characteristics. The authors showed that RAS activation in PTEN-null cells resulted in EMT, and that these EMT-induced cells had CSC characteristics and were responsible for micro- and macro-metastases (Mulholland et al., 2012). Similar results linking EMT and CSC stemness were also reported from uterine cervix cancer cell lines. Interestingly, gene expression analysis of cervical cancer cells indicated that genes required for radioresistance were also up-regulated, including components of the double-strand break (DSB) DNA repair machinery and the metabolism of ROS (Lopez et al., 2012).

**MiRNAs involved in stemness regulation.** MiRNAs play crucial roles in regulating stem cells and CSCs (Huang et al., 2013b). The balance between stemness and differentiation is maintained by the reciprocal regulation miR-145 and the embryonic stem cell genes Nanog, Oct4, Sox2, and Klf4 (Jia et al., 2012; Sureban et al., 2013). In embryonic stem cells, signaling from transcription factors Oct4, Nanog, Sox2, and MYC are regulated with LIN28 to maintain embryonic stem cells in a pluripotent state (Judson et al., 2009). LIN28 inhibits the tumor suppressor activity in and regulates the ALDH1, a marker for breast and ovarian CSCs (Yang, 2010). In breast CSCs, three clusters of miR-200 family miRNAs (miR-200c-141, miR-200b-200a-429, and miR-183-96-182) were significantly down-regulated (Shimono et al., 2009). Recently, miR-22 was found to suppress the expression of miR-200 family members in breast CSCs via direct targeting of chromatin-remodeling enzymes such as ten-eleven translocation (TET) family members. Inhibition of TETs leads to hypermethylation of the miR-200 promoter and induction of EMT and stemness in breast CSCs (Song et al., 2013). In hepatocellular CSCs, the expression of miR-181 is involved in the regulation of differentiation by targeting transcription factors CDX2 and GATA6 (Ji et al., 2012; Meng et al., 2012). In pancreatic CSCs, a signature of many miRNAs, including miR-99a, miR-100, miR-125b, miR-192, and miR-429, involved in self-renewal and differentiation is shown (Jung et al., 2011). Furthermore, miR-34 down-regulation and restoring of miR-34 in pancreatic CSCs repress self-renewal by blocking the expression of the BCL2 and Notch signaling pathways (Ji et al., 2009).

**LncRNAs involved in stemness regulation.** LncRNAs that are associated with canonical signaling pathways were identified via bioinformatics and microarray analysis to play a role in stemness properties. The Shh–GLI1 pathway associated with lncRNA-Hh and transcriptionally regulated by Twist directly targets GAS1 to stimulate the activation of Hh signaling. The activated Hh increases GLI1 expression and enhances the expression of Sox2 and Oct4 to play a regulatory role in CSCs maintenance (Zhou et al., 2016b). In HCC, lncRNA calmodulin-binding transcription activator 1 (lncCAMTA1) promotes proliferation and CSC-like properties of liver cancer cells by inhibiting CAMTA1. High lncCAMTA1 expression in HCC indicates poor clinical outcome (Ding et al., 2016).

The above-cited data highlight the critical role of many miRNAs and lncRNA in regulating CSC self-renewal.

**Cooperation between miRNAs and lncRNAs in EMT**

MiRNAs and lncRNAs can cooperate with each other in a miRNA-lncRNA network to regulate EMT. LncRNAs contribute to EMT in multifaceted modes of action including (Table 1) chromatin remodeling, transcriptional control, alternative splicing, competing endogenous RNAs (ceRNA)/miRNA sponges, regulation of miRNA stability, regulation of protein translation, and regulation of protein degradation and function (Dhamija and Diederichs, 2016). CeRNAs are endogenous coding or non-coding transcripts including lncRNAs, circular RNAs, and pseudogenes that share sequences with common micro-RNAs (microRNA response elements [MREs]). CeRNAs bind and sequester miRNAs to protect their target miRNAs from being degraded. LncRNAs have been shown to regulate EMT through their ability to act as ceRNAs for EMT-regulatory miRNAs. In pancreatic carcinomas, H19 promotes cancer cells invasion by increasing expression of its target HMGA2-mediated EMT through antagonizing miRNA oncopressor let-7 by endogenous competition (Ma et al., 2014). In colorectal cancer, H19 also functions as a ceRNA for miR-138 and miR-200a, with derepression of their targets Vimentin, Zeb1, and Zeb2 (Liang et al., 2015). In gastric cancer, HOTAIR induces EMT by competing with miR-331–3p through the HER2/Akt/HSF-1/Slug pathway, miR34a through the HGF/C-Met/Snail pathway, and miR-568 to maintain NFAT5 expression, which promotes...
| LncRNAs symbol | Official full name | Principal functions | Mechanisms of action | Cancer type | Expression | References |
|----------------|-------------------|---------------------|----------------------|-------------|-----------|------------|
| **ANRIL/CDKN2B-AS** | Antisense RNA in the INK4 locus | Migration, Invasion, EMT | Decreases the expression of E-cadherin and increases N-cadherin and Vimentin expression. Histones modifications. | Pancreas, ovary, lung, liver | Up | Chen et al., 2017; Aguilo et al., 2016 |
| **BANCR** | BRAF-activated non-protein coding RNA | EMT, Migration, Metastasis | Induces EMT through the MEK/ERK pathway, Promotes EMT and metastasis by regulating EMT marker expression. | Stomach, colon thyroid, lung | Up | Liu et al., 2016; Sun et al., 2014 |
| **BCYRN1/BC200** | Brain cytoplasmic RNA 1 | Migration, Invasion, Metastasis | Improves expressions of the key metastasis-supporting proteins MMP-9 and MMP-13. Functions as a molecular sponge for let-7, antagonizes its functions, and leads to derepression of its endogenous targets HMG2 and c-Myc. | Lung | Up | Iacoangeli and Tiedge, 2013; Hu and Lu, 2015 |
| **CCAT1** | Colon cancer–associated transcript 1 | Migration, Invasion | Regulates SPRY4 in nucleus and HOXB13 as a molecular decoy for miR-7 in cytoplasm. Functions as a molecular sponge for let-7; antagonizes its functions, and leads to derepression of its endogenous targets HMG2 and c-Myc. | Esophagus, liver | Up | Zhang et al., 2017; Deng et al., 2017 |
| **CCAT2** | Colon cancer–associated transcript 2 | Migration, Invasion, Metastasis | Activates Wnt pathway, Induces chromosomal instability. | Colon | Up | Ling et al., 2013 |
| **EFNA3** | Ephrin-A3 | Migration, Angiogenesis | miRNAs inhibition of EFNA3 protein transduction. | Breast | Up | Gomez-Maldonado et al., 2015 |
| **HOTAIR** | HOX transcript antisense RNA | Migration, Invasion, Metastasis | Promotes EMT by suppressing miR-568 to maintain NFAT5 expression, Promotes EMT through regulating Snail via HER2/AKT/HSF-1/Slug pathway by inhibiting miR-331-3p, by silencing miR-34a, or by binding to PRC2 (gastric cancer), Inhibits WIF-1 expression and activates Wnt pathway to induce EMT (esophageal cancer), Down-regulates E-cadherin and induces EMT (hepatocellular carcinoma). | Esophagus, stomach, colon, liver breast, lung | Up | Gupta et al., 2010; Liu, 2014 |
| **HOTTIP** | HOXA distal transcript antisense RNA | Migration, Invasion, Metastasis | Regulates Wnt/β-catenin pathways. | Liver, pancreas, tongue | Up | Sang et al., 2016 |
| **HULC** | Hepatocellular carcinoma Up-regulated lncRNA | EMT, Migration | Activates PI3K/Akt/mTOR or TNF-α pathway, and binds to miR-200a/3p-ZEB1 | Stomach, colon, liver, pancreas, bone | Up | Xie et al., 2013 |
| LncRNAs symbol | Official full name | Principal functions | Mechanisms of action | Cancer type | Expression | References |
|----------------|-------------------|---------------------|----------------------|-------------|-----------|-----------|
| **H19**        | H19 imprinted maternally expressed transcript | Metastasis EMT Metastasis | –Promotes EMT by interacting with EZH2 and repressing E-cadherin expression<br>–Promotes EMT as ceRNA for miR-138 and miR-200a<br>–Chromatin modifications<br>–H19 acts as sponge of let-7, miR-138, miR200a, and miR-141, and generates miR-675 | Breast, stomach, colon, liver, lung, pancreas, bladder | Up | Matouk et al., 2014<br>Ma et al., 2014<br>Liang et al., 2015 |
| **LncRNA-ATB** | LncRNA-activated by TGFβ | EMT Invasion Metastasis | –Activated by TGFβ; binds to miR-200a, 200c or 200s; up-regulates Zeb1 and/or Zeb2 and ZNF-217 and 36 to induce EMT and invasion<br>–Involves miR-145/HIF-1α, Nanog, Sox2, and Oct4 signaling pathway<br>–Inhibits miR-205 and prevents Zeb2 degradation | Stomach, colon, liver, prostate, breast and kidney | Up | Yuan et al., 2014<br>Shi et al., 2015a |
| **Lin-RoR**    | Long intergenic non-protein coding RNA, regulator of reprogramming | EMT Invasion Metastasis | –Mediates TGFβ-induced cell migration, invasion, and EMT | Breast | Up | Zhou et al., 2016b<br>Takahashi, 2014 |
| **LncRNA-HIT** | HOX transcript induced by TGFβ | EMT Migration Invasion Metastasis | –Mediates TGFβ-induced cell migration, invasion, and EMT | Breast | Up | Richards et al., 2015 |
| **LncRNA-Dreh**| LncRNA down-regulated expression by HBx | EMT | –Inhibits metastasis by repressing Vimentin expression and changing the normal cytoskeleton structure<br>–Acts through IL-6/STAT3 signaling | Hepatocellular carcinoma | Down | Huang et al., 2013a |
| **LncRNA-TCF7**| LncRNA T-cell factor-7 | EMT Invasion | –Induces EMT through the TGFβ1-ZEB2NAT-ZEB2 axis in CAFs<br>–Mediates TGFβ-induced EMT via Suz12, or promotes EMT by activating Wnt/β-catenin signal pathway<br>–Activates EMT and cell migration–related genes | Liver | Up | Wu et al., 2015 |
| **LncRNA-ZEB2NAT** | LncRNA ZEB2NAT | EMT | –Promotes proliferation and metastasis of osteosarcoma cells by activating the COX-2 gene | Bone (osteosarcoma) | Up | Qian et al., 2016 |
| **MALAT1**     | Metastasis-associated lung adenocarcinoma transcript 1 | Migration EMT Invasion Metastasis | –Mediates TGFβ-induced EMT via Suz12, or promotes EMT by activating Wnt/β-catenin signal pathway<br>–Activates EMT and cell migration–related genes | Lung, breast, uterine cervix, prostate, pancreas, kidney | Up | Gutschner et al., 2013<br>Meseure et al., 2016b |
| **MVIH**       | Microvascular invasion in hepatocellular carcinoma | Angiogenesis Metastasis | –Interplays with miR-199a | Liver, breast, lung | Up | Lei et al., 2016 |
| **NEAT1**      | Nuclear paraspeckle assembly transcript 1 | Migration Invasion | –Interplays with miR-204/ZEB1, miR-377-3P-E2F3, FUS miR-548, and miR-449b | Lung, liver, colon, prostate, bladder | Up | Zeng et al., 2014 |
| **PACERR**     | PTGS2 antisense NFkB1 complex-mediated | Migration Metastasis | –Promotes proliferation and metastasis of osteosarcoma cells by activating the COX-2 gene | Bone (osteosarcoma) | Up | Qian et al., 2016 |
| LncRNAs symbol | Official full name | Principal functions | Mechanisms of action | Cancer type | Expression | References |
|----------------|-------------------|---------------------|----------------------|-------------|------------|------------|
| **SPRY4-IT1** | SPRY4 intronic transcript 1 provided | EMT Migration Invasion | –Regulates E-cadherin and Vimentin expression and promotes tumor proliferation and metastasis by affecting the EMT process | Stomach, brain, lung | Up | Shen et al., 2016, Sun et al., 2014, Zhang et al., 2017 |
| **PVT1** | Plasmacytoma variant translocation gene (also known as Pvt1 oncogene) | EMT | –Deregulates the expression of miR-200 family | Breast | Up | Conte et al., 2017, Paci et al., 2014 |
| **LEIGC** | LEIGC | EMT | –Acts as tumor suppressor by inhibiting EMT | Stomach | Down | Han et al., 2014 |
| **TreRNA** | Translation regulatory lncRNA | EMT Migration Invasion | –Interacts, directly or indirectly, with the 3’UTR of E-cadherin mRNA | Breast | Up | Gumireddy et al., 2013 |
| **TUG1** | Taurine up-regulated 1 | EMT | –Elevates Zeb2 expression by negatively regulating miR-145 expression –miR-145/Zeb2 axis mediates TUG1 function on EMT and radioresistance –Decreases the expression of E-cadherin and increases N-cadherin, Vimentin, and Fibronectin expression | Bladder, colon | Up | Tan et al., 2015, Sun J et al., 2016 |
| **UCA1** | Urothelial cancer–associated 1 | EMT Migration Invasion | –Promotes migration and invasion via hsa-miR-145/Zeb1/2–FSCN1 pathway | Esophagus, bladder | Up | Li et al., 2014a, Wang et al., 2014b |
| **ZEB2-AS1** | ZEB2 antisense RNA 1 | EMT Metastasis | –Regulates the expression of EMT markers | Hepatocellular carcinoma | Up | Lan et al., 2016 |
| **ZEB1-AS1** | ZEB1 antisense RNA 1 | EMT | –Induces EMT by up-regulating Zeb1 expression | Lung | Up | Li et al., 2017 |
invasion via EMT (Liu et al., 2014). *PVT1* is implicated in deregulated expressions of the miR-200 family members, which play a key role in EMT by inhibiting Zeb1/2 and up-regulating E-cadherin (Conte et al., 2017; Paci et al., 2014). *TUG1* decreases miR-145 expression and activates Zeb2 (Tan et al., 2015). In HCC, *lncRNA-ATB* promotes EMT by competing with the miR-200 family members and up-regulating Zeb1 and Zeb2 (Shi et al., 2015a). In bladder cancer, *UCA1* promotes EMT by inhibiting miR-145 and derepressing Zeb1/2 (Xue et al., 2016). In HCC, *linc-ROR* induces EMT by modulating hypoxia through a miR-145/HIF-1α signaling pathway, and by inhibiting miR-205 and preventing Zeb2 degradation (Takahashi et al., 2014).

Overall, this lncRNA-miRNA cross talk suggests the existence of a complex regulatory network in cancer and implies the possibility of cancer diagnosis and therapy using this panel of networks (Cao et al., 2017).

**Therapeutic resistance**

Tumor complexity is perpetuated by the interaction between cancer cells and their microenvironment, contributing to therapy resistance. Tumor metastasis brings about another layer of complexity, as the TME changes relative to the primary site. Moreover, tumor adaptation to the surrounding microenvironment is influenced by selective pressure applied by drug therapy (Smith et al., 2016).

CAFs induce cancer progression as well as resistance to cancer therapies through secretion of proteins, exosomes, and ECM remodeling factors (Fu Het al., 2016). In addition, TAMS secrete E2, IL-10, TGFβ, indoleamine-pyrrole 2,3-dioxigenase, CCL17, CCL18, and CCL22 in TME, which create immunosuppressive conditions by inhibition of Th1 immune response (Komohara Yet al., 2014; Allavena et al., 2008). It has been suggested that these immunosuppressive factors secreted by TAMS induce therapeutic resistance (Son et al., 2017).

Therapies targeting endothelial and immune-evasive cells also present challenges when tumor signaling adapts (Smith et al., 2016). Doxorubicin therapy induced thymic endothelial cell expression of IL-6 and tissue inhibition of TIMP-1, providing tumor cells with a protective niche within the thymus tissue (Junttila et al., 2013). Following the administration of anticancer therapy, hypoxia increases tumor growth and survival.

The reason that a broader therapeutic strategy of targeting both epithelial cancer cells and their microenvironment is starting to show promise may be because cells undergoing EMT are addressed, as well as the source of paracrine mediators of tumor progression and differentiation (Smith et al., 2016).

The role of EMT in therapy resistance and tumor recurrence is evident in several tumors (Smith et al., 2016). Two recent reports in mouse models of breast and pancreatic cancers revealed that cancer cells that have undergone an EMT support metastasis formation upon chemotherapy. Authors employed genetic lineage tracing and manipulation of the expression of major EMT-TFs Snail or Twist to demonstrate that EMT is required for chemotherapy resistance (Fischer et al., 2015; Zheng et al., 2015). Additionally, Snail may promote tumor aggressiveness in androgen-dependent prostate cancer cells through induction of EMT and acquiring of neuroendocrine-like morphology (McKieithen et al., 2010). These findings are particularly interesting, considering that neuroendocrine differentiation in prostate cancer cells increases with tumor progression and the development of androgen refractoriness. Moreover, Twist has been identified as negative regulator of ER, which participates in antihormonal therapy resistance in breast cancer cells (Vesuna et al., 2012).

The identification of EMT process as a critical regulator of the CSC-like phenotype offers an opportunity to investigate a possible mechanistic mechanism of drug resistance. Accumulating evidence indicates that conventional anticancer therapies often fail to eradicate cancer cells that have entered into CSC state via activation of the EMT process, thereby permitting CSC-mediated clinical relapse (Shibue and Weinberg, 2017). In fact, Snail and Slug are critical for cancer cells to acquire stem cell characteristics, which are associated with radiotherapy or chemotherapy resistance by reducing apoptosis (Kurrey et al., 2009).

However, EMT as a complex bidirectional process (EMT/MET) seems difficult to target. Blocking cancer cell invasion or inhibiting EMT may be useful in the early stage of cancer dissemination. But once cancers have disseminated from the primary tumor site, inhibiting EMT may be counterproductive, since it is beneficial for MET (Cao et al., 2017). Thus, full understanding of the events driving the interactions between cancer cells that undergo EMT, as well as their microenvironment, is of crucial importance in overcoming treatment resistance and improving patient outcome (Kharaishvili et al., 2014).

Furthermore, aberrant expression of ncRNAs in several cancers attributes to inherent defects or stress-responsive variations and mediates cellular signaling that compensates for unfavorable molecular events, which prevent the anticancer agents from exerting their desired effects on their cellular targets. Alternatively, ncRNAs may regulate cancer therapeutic sensitivity by affecting drug accessibility to neoplastic cells and in vivo drug metabolism. In addition, dysregulation of ncRNA expression in TME stromal cells can impair the responsiveness of cancer cells to appropriate therapies (Jia et al., 2016).

Recent data confirmed that miR-21 sustains in EMT in HER2-positive breast cancer and targets PTEN and programmed cell death protein 4 (PDCD4). These results support that miR-21-mediated epigenetic silencing of both tumor suppressor genes, particularly PTEN, could be an important mechanism of resistance to trastuzumab chemotherapy in patients with HER2-positive tumors. As a result, the authors demonstrated that the down-regulation of PTEN and PDCD4 differentially influenced the sensitivity of HER2-positive breast cancer cells to current chemotherapy. These results indicate that miR-21 could serve as a comprehensive predictive marker of response to such therapy for HER2-positive breast cancer patients (De Mattos-Arruda et al., 2015).

Thus, understanding ncRNA-related mechanisms’ underlying resistance to anticancer therapeutics can enhance the development of drug-sensitizing strategies targeted against or based on these ncRNAs.

**Conclusion And Future Perspectives**

Taken together, the above data reveal multiple reciprocal interactions between tumor microenvironment and ncRNAs (miRNAs and lncRNAs) in driving cancer cell plasticity and heterogeneity, resistance to therapies, and metastatic spread. EMT, ncRNAs, and microenvironment regulatory networks are crucial for predicting metastasis. An increasing number of ncRNAs have been found to be dysregulated in various malignant tumors and may serve as potential biomarkers and targeted therapies for cancer. A better
understanding of molecular and cellular mechanisms implicated in this reciprocal cooperation is mandatory to identify pertinent prognostic and predictive biomarkers and to develop new multi-targeted therapies. Although many molecular pathways are common to oxidative stress, hypoxia, inflammation, EMT, metabolic switch, immunosuppression, and resistance to therapies, combined strategies seem preferable considering the too-large number of stromal and cancer cells reprogramming and remodeling mechanisms. Actually, the most promising pharmacological approaches that allow both targeting of cancer cells and restoring an immunocompetent microenvironment could associate conventional antitumor cells therapies, inhibitors of plasticity, inflammation, hypoxia, de novo angiogenesis, and epigenetic reprogramming with immunomodulation, including immune checkpoint inhibitors and chimeric antigen receptors.

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