Role of miRNA clusters in epithelial to mesenchymal transition in cancer

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1. ABSTRACT

Epithelial to mesenchymal transition (EMT) is a multistep biological process in which epithelial cells acquire characteristics of mesenchymal cells. Inappropriate activation of EMT contributes to the acquisition of pro-metastatic characteristics and cancer progression. EMT process involves the downregulation of epithelial markers (*EpCAM, CDH1*) and upregulation of mesenchymal markers (*VIM, CDH2*) and EMT-transcription factors (*ZEB1/2, TWIST1/2, SNAI1, SLUG*). MicroRNAs, a class of non-coding RNA post-transcriptionally govern gene expression by binding to the target mRNAs. A large proportion of miRNAs occur as miRNA clusters consisting of two or more miRNA coding genes. MiRNA clusters are reported to regulate diverse biological functions, including EMT. This comprehensive review discusses the role of miRNA clusters in EMT.

2. INTRODUCTION

An epithelial to mesenchymal transition (EMT) is a biological process in which epithelial cells lose their polarity and cell-cell adhesion properties, and gain migratory and invasive properties to become mesenchymal cells (1). Early changes in EMT include loss of cell to cell adhesion and the advanced stages are characterized by degraded

basement membrane and cellular delamination (2). EMT engages new transcriptional programs that lead to epithelial to mesenchymal transition. Thus, the completion of EMT is marked by the degradation of the underlined basement membrane, formation of mesenchymal cells and migration of these cells away from its origin (epithelial layers) (3). During EMT, polarized epithelial cells undergo several biochemical changes and acquire mesenchymal characters such as enhanced migration, invasiveness and increased extracellular matrix (ECM) production (4).

EMT process was first observed by Elizabeth Hay in 1960 when working with chicken embryogenesis (1). Epithelial cells are characterized by the presence of adherent and tight junctions, desmosomes and apicobasal polarity (5). EMT is classified as type 1 (organ development and embryogenesis), type 2 (wound healing, tissue regeneration, and organ fibrosis) and type 3 (cancer invasion and metastasis) (6). From a clinical perspective, EMT is associated with self-renewal, resistance to chemotherapy and radiotherapy, enhanced migration and invasion, anoikis resistance, evasion of the immune system and metastasis of cancer cells.

3. MOLECULAR PATHOGENESIS OF EMT

EMT involves (i) dissolution of cell junctions including tight junctions, (ii) destabilization of adherence junction, and (iii) loss of apicobasal polarity. Cytoskeletal changes include the reorganization of cortical actin and the formation of actin-rich membrane projections (7). Formation of actin stress fiber is characterized by activation of Rho GTPases namely Ras homolog gene family, member A (*RhoA*) and the Rac family small GTPase1 (*RAC1*) and Cell division cycle 42 (*CDC42*) (8). Directional cell polarity is important for cell migration and is achieved by the relocalization of proteins namely protein associated with tight junctions (PATJ) to the leading edge of the cells. RAC1 and CDC42 promote actin polymerization leading to the formation of membrane protrusions facilitating migration. Localization of RhoA to the rear end of the cells results in disassembly of adhesion complexes and cell retractions resulting in enhanced migration (8).

The downregulation of *CDH1*, cytokeratins, claudins, γ-catenin, and *ZO-1* are often observed during EMT. The most common upregulated proteins during EMT include N-cadherin (*CDH2*), vimentin (*VIM*), fibronectin, α smooth muscle actin (*ACTA2*), matrix metalloproteinases (MMPs) and integrins (5). Additionally, there is also the upregulation of EMT-transcription factors (EMT-TFs) such as Zinc finger E-box binding homeobox 1 (ZEBs), Snail Family Transcriptional Repressor 1 (SNAIL), Snail Family Transcriptional Repressor 2 (SLUG), and Twist Family BHLH Transcription Factor (TWIST) (9). EMT can be induced by cytokines, hypoxia, growth factors from tumor microenvironment, metabolic changes, and immune responses (innate and adaptive) via activation of signaling pathways (10, 11). EMT can also be induced by epigenetic modifications, alternative splicing and non-coding RNAs (microRNAs and long-non-coding RNAs) (1, 6, 10, 12–14).

Many signaling pathways activate EMT by inducing the expression of zinc finger proteins (SNAIL family), basic helix loop helix (TWIST family) and zinc finger E box binding proteins (ZEB family) (1). Transforming Growth Factor Beta (TGF-β), receptor tyrosine kinases (RTKs), integrin, WNT, NOTCH, Hedgehog, hypoxia-inducible factor 1α (HIF1α), and Janus kinase2/Signal Transducer and Activator of Transcription (JAK/STAT) pathways are reported to regulate EMT cascade (15). The EMT-TFs recruit co-activators and co-repressors to target genes and alters the rate of transcription. Among the genes, the most commonly targeted include genes belonging to the cell to cell adhesion such as cadherins. The loss of *CDH1* is an important and critical step in the induction of EMT. Downregulation of claudin and occluding (tight junctions), desmoplakin and plakophilin (desmosomes), cytokeratins and intermediate filaments were also reported to have occurred during EMT (15). Tumor necrosis factor (TNFα) bound to TNF receptor superfamily member 1A (TNFR) can activate nuclear factor kappa B subunit 11 (NFkB) via IkappaB (IkB) and induces the expression of *SNAIL1*/2, *ZEB1*/2, and *TWIST1* (16). Interleukin 6 (IL6), via binding to IL6R, induces the expression of *TWIST1* (17). Epidermal growth factor (EGF) can induce EMT by upregulation of MMP3 via the

EMT State	Epithelial Phenotype	Early hybrid	Late Hybrid	Mesenchymal Phenotype
Surface markers	EpCAM, Cdh1	TN, CD106	CD51, CD106/51	CD51/61, TP
Markers	Krt5, Krt14, Dsg2, Esrp1/2	Krt5, Krt14, Vim, Cdh2	Krt5, Krt14, Vim, Pdgfrb, Fap, Cdh2	Vim, Aspn, Cdh2, Fap, Mmp19, Lox
TFs	Trp63, Klf4, Ovol1, Grhl1-3	Trp63, Grhl1-3, Zeb1/2, Twist1/2, Snai1	Zeb1/2, Twist1/2, Snai1	Prrx1, Zeb1/2, Twist1/2, Snai1

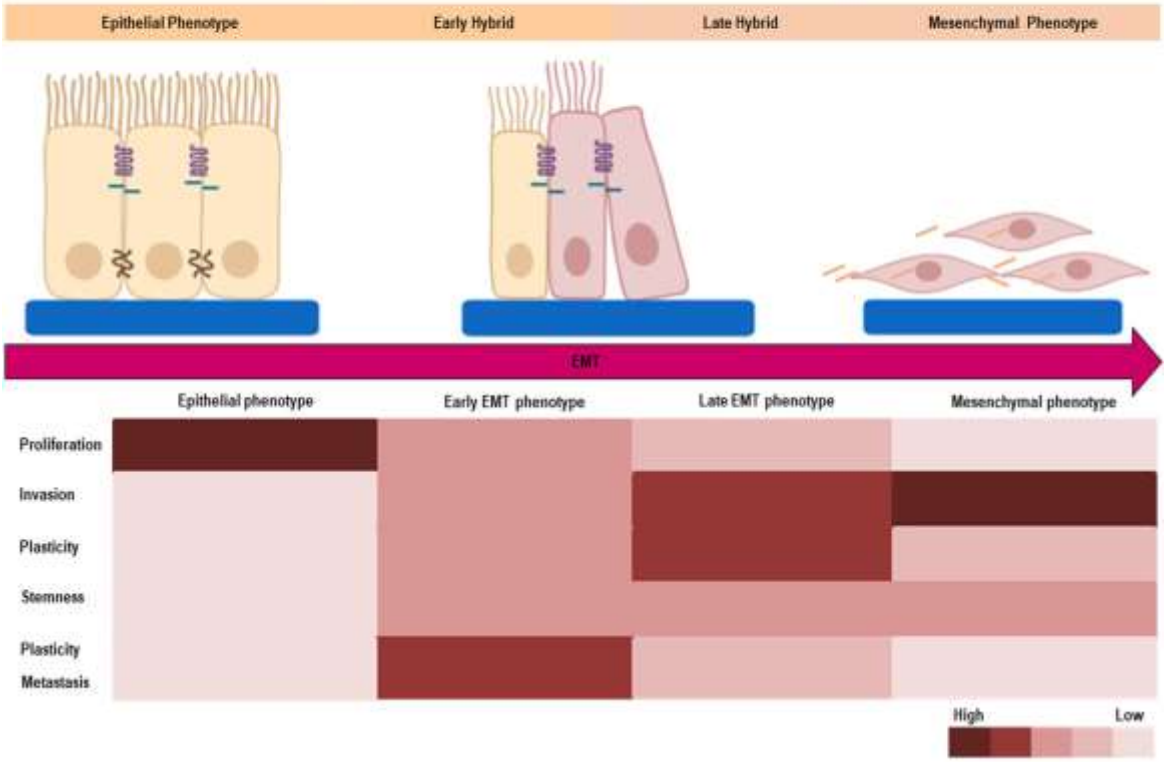

Figure 1. Schematic representation of characteristics of epithelial to mesenchymal. An EMT occurs through distinct cellular states from transition of polarized epithelial cells to mobile mesenchymal cells. Different epithelial and mesenchymal markers and transcriptional factors (TFs) are shown (14, 196).

JAK/STAT pathway (18). Induction of HIF1α via Phosphoinositide-3-Kinase- AKT Serine/Threonine Kinase 1-Mammalian Target of Rapamycin (PI3K-AKT-mTOR) can induce EMT (19). Pro-EMT nature of Rat sarcoma-mitogen-activated protein kinase 1 (RAS-MAPK) and MAPK1-mitogen-activated protein kinase 1(MKK)-p38-SMAD is also reported (20, 21). TGF-β by binding to TGFβR can induce the expression of *SNAIL, SLUG, ZEB1/2, and TWISTs* promoting EMT. WNT1-Beta-catenin axis is reported to promote EMT via activating *SNAIL* expression. Notch signaling induces EMT through activation of *SNAIL, SLUG, ZEB1/2* and *TWIST* (15). The induction of SNAIL1 and TWIST1 by HIFα also induces EMT (22). Similarly, extracellular matrix protein can also induce EMT. For example, collagen 1 via activation of SRC Proto-Oncogene (SRC) and MAPK1 can induce *SNAIL1* expression (23). The induction of *TWIST1* via Lysyl oxidase (LOX) by CD44 has also been reported (24) (Figure 1).

4. miRNA CLUSTER

MicroRNAs (miRNAs) are a class of non-coding RNAs used by cells for fine-tuning the expression of genes in a variety of cell and tissue types (25). miRNAs bind to the target mRNA via

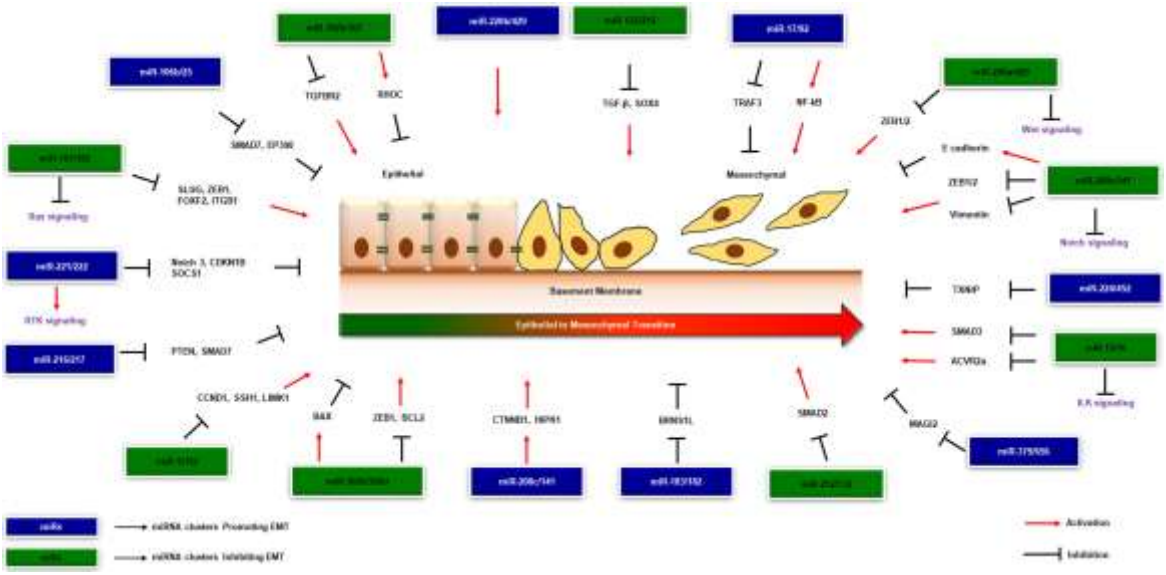

Figure 2. miRNA Cluster regulates EMT pathway *via* targeting different genes and associated signaling pathways.

complementary base-pairing and affect its expression by mRNA degradation or translational repression (25). Furthermore, it is clear that miRNAs often show deregulated expression leading to the acquisition of multiple cancer hallmarks (26). miRNA clusters consist of two or more miRNAs encoding genes transcribed together in the same orientation without having any miRNAs in the opposite direction (27). More than thirty percent of miRNAs occur in clusters. Chromosome 19 is the largest miRNA cluster in the human genome consisting of 46 miRNAs located in chr19q13.42 (28). Since the miRNA cluster consists of many miRNA encoding genes, its dysregulation can affect multiple cellular functions as opposed to single miRNA alteration. Similar to individual miRNAs, aberrant expression of the miRNA cluster is also reported in multiple cancer. In this review, we discuss the role of miRNA cluster in the multi-step EMT program during carcinogenesis.

4.1. miRNA Cluster and EMT

There are several miRNA clusters whose expression is altered contributing to the induction of EMT in different cancer conditions. For example, the miR-200c/141 cluster promotes EMT in breast cancer by targeting Homeodomain Interacting Protein Kinase 1 (HIPK1) and by activating *CTNNB1* (29). MiR-221/222 promotes EMT in breast cancer by targeting Phosphatase and Tensin Homolog (*PTEN*), Suppressor of Cytokine Signaling 1(*SOCS1*), Cyclin-Dependent Kinase Inhibitor 1B (*CDKN1B*) and Notch Receptor 3 (*NOTCH3*) (30–32). Similarly, miR-183/182 activates EMT in breast cancer by targeting Growth Hormone Receptor (*GHR*) (33). MiR-216/217 induces EMT by targeting *PTEN* and SMAD Family Member 7 (*SMAD7*), resulting in the activation of PI3K/AKT signaling and sorafenib resistance in liver cancer (34). MiR-17/92 cluster modulates NF-kB signaling via targeting of TNF Receptor Associated Factor 3 (*TRAF3*) in gastric cancer to induce EMT (35) (Figure 2).

Several studies have shown the inhibition of EMT by miRNA clusters. For instance, miR-15a/16 inhibits EMT in prostate cancer by suppressing TGF-β (36). MiR-200c/141 inhibits EMT in colon and lung cancer by targeting Achaete-Scute Family BHLH Transcription Factor 2 (*ASCL2*) and Forkhead Box F2 (*FOXF2*) respectively (37, 38). *FOXF2* is also inhibited by the miR-183/182 cluster in colon cancer (37). MiR-17/92 inhibited EMT by downregulation of CyclinD1 (*CCND1*), Slingshot Protein Phosphatase 1 (*SSH1*), LIM Domain Kinase 1

Table 1. miRNA cluster promoting EMT

miRNA Cluster	Cancer	Signaling/Gene	Reference
miR-200c/141	Breast Cancer	Targets *HIPK1* and activated β-catenin	(29)
miR-17/92	Gastric Cancer	Targets *TRAF3* and modulates NF-kB	(35)
miR-221/222	Breast Cancer	Targets *PTEN* and activating Akt/NF-kB/Cox-2 pathway	(30)
miR-183/182	Breast cancer	Targets *BRMS1L*	(33)
miR-224/452	Melanoma	Targets *TXNIP*	(40)
miR-221/222	Breast Cancer	Targets *SOCS1* and *CDKN1B*	(31)
miR-106b/25	Breast Cancer	Targets *EP300*	(41)
miR-379/656	Lung Adenocarcinoma	Targets *MAGI2*	(42)
miR-200b/429	Breast Cancer	-	(43)
miR-216/217	Liver Cancer	Targets *PTEN* and *SMAD7*	(34)
miR-106b/25	Breast Cancer	Targets *SMAD7* and activates TGF-1 alpha	(44)
miR-221/222	Breast Cancer	*Notch3*	(32)

Abbreviations: HIPK1, homeodomain interacting protein kinase; TRAF3, TNF receptor associated factor 3; PTEN, phosphatase and tensin homolog; BRMS1L, BRMS1 Like Transcriptional Repressor; TXNIP, Thioredoxin Interacting protein; SOCS1, Suppressor of Cytokine Signaling 1; CDKN1B, Cyclin Dependent Kinase Inhibitor 1B; EP300, E1A binding protein 300; MAGI2, Membrane Associated Guanylate Kinase; SMAD7, SMAD Family Member 7.

(*LIMK1*), Fibroblast Growth Factor 4 (*FGFD4*) and RhoGTPase (39) (Tables 1 - 2).

4.2. *SLUG* and miRNA cluster

Snail Family Transcriptional Repressor 2 (*SNAIL2*), commonly known as the SLUG is located at 8q11.21. SLUG is overexpressed and amplified in numerous cancers is reported to promote cell migration, invasion, metastasis, cell cycle progression and resistance to apoptosis (52–57). SLUG is a transcription factor belonging to the zinc finger family induces transcriptional repression of *CDH1* and is anti-apoptotic in nature. Highly aggressive tumors show overexpression and enhanced activity of SLUG. Both SNAIL and SLUG promote invasion and metastasis by altering the expression of *CDH1* and *VIM* (58). They inhibit *CDH1* by binding to the E-box sequences present in its promoter region (59). Further, SLUG is also capable of downregulating Claudin-1 (*CLDN1*) in Madin-Darby canine kidney (MDCK) cells (60). SLUG induces cell migration and invasion via TGF-β signaling (61). SLUG utilizes the SNAG domain to suppress target gene expression by recruiting histone deacetylases. Elevated SLUG expression is connected to *CDH1* downregulation, induction of EMT, advanced tumor grade, lymph node metastasis and poor survival (62).

SLUG participates in TWIST1 induced EMT pathways by repressing the transcription of *CDH1* (52, 63). Many of the miRNA clusters downregulate SLUG expression and inhibit EMT. For instance, miR-17/92 cluster expression is correlated with inhibition of SLUG and induction of *CDH1* with inhibitory effect on EMT (39). MiR-34, a member of the miR-34b/c cluster acts as a tumor suppressor and inhibitor of EMT by targeting SLUG (64). MiR-96/183 promotes the expression of key EMT inducers such as ZEB1, ZEB2, SNAIL2, MMP2, and MMP9 by suppressing the breast cancer metastasis suppressor 1-like (*BRMS1L*) (33). MiR-183/182 is another miRNA cluster that promotes EMT by promoting the expression of mesenchymal genes and EMT-TFs such as SNAIL, and SLUG (49, 65). In colorectal cancer, miR-182 targets *FOXF2* and induces growth and migration of cancer cells (66). MiR-182, along with miR-203, acts as an inducer of EMT by targeting SLUG expression in prostate cancer (67). MiR-183 and miR-96 are a suppressor of EMT by targeting ZEB1, SLUG, Integrin beta 1 (*ITGB1*), and Kruppel-like factor 4 (*KLF4*) (49). Taken together, SLUG is an important inducer of EMT whose expression is upregulated in cancer via altered expression of miRNA clusters.

Table 2. miRNA cluster inhibiting EMT

miRNA Cluster	Cancer	Signaling/Gene	References
miR-15/16	Prostate Cancer	Target *SMAD3*and *ACVR2A*	(36)
miR-302b/302d	Endometrial carcinoma	Target *ZEB1*, *Bcl-2* and promoted expression of BAX	(45)
miR-302b/367	Colon cancer	Inhibiting *TGFBR2* and activating RHOC	(46)
miR-302b/367	Melanoma	Inhibiting *TGFBR*2 and activating RHOC	(46)
miR-132/212	Prostate Cancer	Target *SOX4* and inhibits TGF-beta	(47)
miR-17/92	Prostate Cancer	Decreased expression of cyclin D1, *SSH1 LIMK1* and *FGD4*	(39)
miR-212/132	Cervical Cancer	Downregulate SMAD2 and suppresses G1/S transition	(48)
miR-200c/141	Lung cancer	Target *FOXf2*	(37)
miR-183/182	Lung cancer	Target *FOXf2*	(37)
miR-200c/141	Colon cancer	Target *ASCL2*	(38)
miR-183/182	Overexpressed p21 colon and breast cancer cell lines	Target *SLUG, ZEB1,ITGB1, KLF4*	(49)
miR-200a/429	Mammary carcinoma	Target *ZEB1* and *ZEB2*	(50)
miR-200c/141	Biliary tract cancer	Positively correlated with CDH1 and negatively correlated with VIM	(51)

Abbreviations: SMAD3, SMAD family member 3; ACVR2A, Activin A Receptor Type 2A; ZEB1, Zinc finger E-box binding homeobox1; TGFBR2, transforming growth factor beta receptor 2; RHOC, Ras homolog family member C; SOX4, SRY-Box 4; TGF-β1, transforming growth factor beta 1; SSH1, Slingshot protein phosphatase 1; LINK1, LIM domain kinase 1; FGD4, FYVE, RhoGEF And PH Domain Containing 4; FOXF2, forkhead box F2; SLUG, Snail Family Transcriptional Repressor 2; ZEB, Zinc Finger E-Box Binding Homeobox; ITGB1, Integrin Subunit Beta 1; KLF4, Kruppel Like Factor 4; ASCL2, Achaete-Scute Family BHLH Transcription Factor 2; CDH1, E-cadherin, VIM, Vimentin.

4.3. *SNAIL* and miRNA cluster

Snail Family Transcriptional Repressor 1 (*SNAIL1*) is a pro-EMT gene overexpressed in many metastatic cancers promoting cell survival and migration. SNAIL, via its N-terminal SNAG domain, interacts with and recruits co-repressors and repressors to the promoter region of *CDH1* thereby promoting EMT. Pro-EMT signaling pathways [RTKs, TGF-β, Notch, Wnt, TNF-α, and bone morphogenetic protein 2 (BMP)] along with tumor microenvironment are reported to promote EMT by inducing SNAIL expression. From the clinical perspective, SNAIL expression levels are correlated with tumor grade, metastasis to lymph node and clinical outcome in metastatic cancer. Moreover, SNAIL overexpression is reported to induce metabolic reprogramming and to promote drug resistance, recurrence, and metastasis (68–70).

Emerging evidence suggests crosstalk between miRNA cluster and SNAIL during EMT program. MiR-23a/24/27a located at 19p13.12 is regulated through MAPK and TGF-β signaling. MiR-23a-3p inhibits EMT via TGF-β/Akt/MAPK/Snail axis (71). In bladder cancer, miR-323a-3p/MET proto-oncogene (MET)/SMAD3/SNAIL axis is reported to regulate EMT (72). MiR-106b/25 cluster enhances non-small cell lung cancer (H1299) cell migration and invasion via targeting of F-box and WD repeat domain containing 11 (β-TRCP2) by enhancing the expression of SNAIL (73). MiR-206 of miR-206/133b cluster targets MET and PI3k/Akt/mTOR pathways and suppresses EMT (74). MiR-183 cluster consists of miRs-183, -96 and -182, and is overexpressed in numerous cancers. MiR-182 directly targets metastasis suppressor 1 (*MTSS1*) and induces the proliferation of breast cancer cells (75). As a member of the miR-181 family, miR-181a is associated with cell proliferation and invasion in multiple cancer. MiR-181a is reported as an inducer of EMT in prostate cancer by targeting TGF-β induced factor homeobox (*TGIF2*) (76). In breast cancer, miR-181b-3p acts as a

Table 3. miRNA cluster and signaling pathway

miRNA	Cancer	Target gene/Signaling Pathway	Reference
miR-221/222	Breast Cancer	Tyrosine kinase	(110)
miR-143/145	Breast Cancer	*ERBB3*/tyrosine kinase	(111)
miR-17/92	large B-cell lymphoma	ITIM/tyrosine kinase	(112)
miR-15/16a	Ovarian Cancer	Integrin-linked Kinase pathway	(113)
miR-143/145	Breast Cancer	*PTEN*/RAS Pathway	(114)
miR-221/222	Breast Cancer	*TRPS1*/ RAS Pathway	(115, 116)
miR-106b/25	Breast Cancer	*NEDD4L*/NOTCH signaling	(117)
miR-200c/429	Pancreatic Cancer	Notch	(118)
miR-17/92	Lung Cancer	p38α kinase/wnt signalling	(119)
miR-200a/429	Hepatocellular carcinoma	Wnt signaling	(120)
miR-17/92	Medulloblastoma	Hedgehog signaling	(121)

Abbreviations: ERBB3, Erb-B2 Receptor Tyrosine Kinase 3; ITIM, immunoreceptor tyrosine inhibitory motifs; PTEN, phosphatase and tensin homolog; TRPS1, Transcriptional Repressor GATA Binding 1; NEDD4L, Neural Precursor Cell Expressed, Developmentally Down-Regulated 4-Like, E3 Ubiquitin Protein Ligase

promoter of EMT via SNAIL stabilization by targeting Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Gamma (77). The role of Smad2/3/4-dependent pathway in EMT is reported in gastric cancer. Smad2/3/4 pathway induces the expression of miRNA-181b and targets TIMP metallopeptidase inhibitor 3 (*TIMP3*) to promote EMT and metastasis (78). MiR-200 family consists of anti-EMT miRNAs their expression is important to determine the epithelial phenotypes in cancer. MiR-200 family activates *CDH1* expression by targeting *ZEB1* and *ZEB2* (65). The down-regulation of miR-200 is reported to enhance the expression of SNAIL and SLUG (79). Studies have shown that miR-34/SNAIL/miR-200/ZEB1 can regulate EMT dynamics (80). Inhibition of miR-200c/141 results in the upregulation of *VIM* and *SNAIL* in breast cancer stem cells (29). MiR-424/503 is another miRNA cluster with tumor suppressive function, the downregulation of which is correlated with resistance to chemotherapy in breast cancer (81). Thus, taken together, miRNA clusters are important regulators of SNAIL expression.

4.4. TWIST and miRNA cluster

TWIST1 and *TWIST2* belong to the basic helix-loop-helix (bHLH) transcription factor family. They promote EMT and enhance the motility and dissemination of cancer cells (82). In benign tumors activation of TWISTs favors malignant transformation via inhibition of apoptosis and senescence pathways. TWIST proteins with their bHLH motif recognize E-box and can act as an activator or repressor of target gene expression (83). TWIST overexpression is correlated with aggressive cancer, poor prognosis, metastasis, and poor survival. Pathways such as Wnt, IGF, EGF, TNF-α, IL-17 either induce TWIST expression or stabilize via their target genes (NF-κB, STAT3, and c-MYC) (16, 84–87). Cytokines, chemokines (IL6, EGF) and hypoxia are reported to induce the expression of TWISTs to promote EMT (17, 86, 88).

Many miRNA clusters participate in the TWIST induced EMT program. MiR-15a-3p and miR-16-1-3p belonging to the miR-15 cluster, are reported to inhibit invasion and metastasis of gastric cancer cells by *TWIST1* repression (89). *TWIST1* is also reported to regulate the expression of miRNA clusters. An example includes the regulation of miR-199a/214 cluster expression by *TWIST1* during development (90). In breast cancer, it induces EMT via the miR-373-TXNIP-HIF1α-TWIST signaling axis (91). Both up and down-regulation of the members of the miR-199a/214 cluster are reported to contribute to EMT in cancer (92). Transcription of miR-214 is regulated by *TWIST1* and *ZEB1* (93). MiR-424(322)/503 is another miRNA cluster linked with TWIST. The upregulation of miR-424 in TWIST1 or SNAI1-induced EMT is reported (94). MiR-106b/25 is

an oncogenic cluster in many cancers and has two paralogs in humans namely miR-106b/25 and miR-17/92. MiR-106b is a pro-metastatic miRNA cluster in hepatocellular carcinoma cells (95). Hypoxia is reported to induce EMT via controlling miRNA cluster expression. For instance, Twist/miR-214/CDH1 interaction is promoted by hypoxia in the induction of renal tubular EMT (96). MiR-524-5p is a member of the chromosome19 miRNA cluster (C19MC) which directly targets *TWIST1* to inhibit EMT (97). Taken together, miRNA clusters and the TWIST axis could be a potential target in cancer therapy.

4.5. ZEB and miRNA cluster

ZEB1 and *ZEB2* are located in short arm of chromosome 10 and 2 belonging to zinc finger E-box binding homeobox (ZEB) family. ZEB family induces EMT most often through activating genes such as *CDH2*, Vitronectin (*VTN*) and MMPs. ZEB induced EMT also shows the downregulation of *CDH1*, Claudins, *ZO*-1, and plakophilins. ZEBs are commonly known as Smad interacting protein 1 (SIP1) consisting of two zinc finger clusters and a central homeodomain (98). ZEB induced EMT also involves miRNA clusters. MiR-200c/miR-141 targets *ZEB1* and *ZEB2* thereby inhibiting migration and EMT in head and neck cancer cells (99). Loss of miR-200c/miR-141cluster is important for lymph endothelial invasiveness in 5-fluorouracil resistant cells (100). By targeting members of C terminal binding protein (CtBP)/ZEB complex, miR-141-200c cluster regulates EMT (101). MiR-143/145 is downregulated in multiple cancers and is an EMT and metastatic suppressor. In response to stress, serum starvation or anti-cancer agents, p53 can activate this cluster. This miRNA cluster is suppressed by activated Ras via binding to Ras-responsive element-binding protein (RREB1) (102). MiR-132 suppresses lung cancer cell migration by targeting *ZEB2* (103). MiRNA-23b/27b/24 is an oncogenic miRNA cluster that promotes metastasis of breast cancer by suppressing Prosaposin (PSAP) (104). MiR-23b targets Protein Tyrosine Kinase 2 Beta (*PYK2β*) and suppresses EMT and metastasis in hepatocellular carcinoma (105). MiR23b targets *ZEB1*, and acts as a tumor suppressor preventing migration and invasion of bladder cancer cells (106). MicroRNA-200/ZEB/CDH1 and miR-200/ZEB/TGF-β axis are also reported in cancer (107, 108). MiR-544 is a member of the miR-379/miR-544 cluster and highly expressed in neonatal muscle. MIR-544's role as an oncogene is established in gastric cancer. It promotes invasion of lung cancer cells by targeting *CDH1* and upregulation of *VIM*. MiR-544a induces EMT by activation of WNT signaling in gastric cancer and immune escape in hepatoma cells. Reduction of *CDH1* and upregulation of *VIM*, *SNAI1*, and *ZEB1* by miR-544a induces EMT (109). MiR-544a directly targets *CDH1* and *AXIN2* leading to nuclear translocation and stabilization of *CTNNB1*. These data collectively suggest that the expression of ZEB is regulated by miRNA cluster and that ZEB along with other EMT-TFs induces EMT and metastasis in multiple cancer. Thus, targeting the ZEB-miRNA cluster axis could be used for the management of cancer.

Taken together, a wide array of transcription factors is associated and required to drive the multistep EMT program and are being regulated by a variety of EMT-TFs and signaling pathways. The EMT-TFs acting exclusively or synergistically, and target common pathways to induce EMT. MiRNA clusters reported to regulate multiple signaling pathways associated with EMT are discussed below.

5. miRNA CLUSTERS AND SIGNALING PATHWAYS

Major signaling pathways responsible for the induction of EMT include tyrosine kinases, integrin-linked kinase, RAS, Wnt, Notch, and Hedgehog. miRNA clusters and target signaling pathways are listed in Table 3.

5.1. Tyrosine kinases pathway

Receptor tyrosine kinases (RTKs) are high-affinity transmembrane receptors which bind to growth factors, cytokines, and hormones. RTKs play an important role in growth, proliferation differentiation and movement of cells (122). RTKs, inappropriately regulated, and expressed in many cancer types, are strongly implicated in EMT (15). Binding of growth factors (EGF, FGF, IGF, HGF,

CFC) to RTKs leads to activation of EMT-TFs such as SNAIL, SLUG, ZEB and TWIST via multiple signaling axis notably PI3K-AKT-glycogen synthase kinase 3 beta (GSK3β)-β-catenin axis or RAS-MAPK signaling (15).

The miRNA cluster can either activate or inhibit the expression of tyrosine kinase pathway genes (123). For example, miRNA cluster 23a/24-2 regulates EGFR and c-MET expression in lung cancer. Cancer cell invasion and metastasis are driven by c-MYC induced miR-23a/27a cluster (124). The treatment of NSCLC cells by TGF-β1 activates miR-134/miR-487b/miR-655 cluster. MiR-134/miR-487b/miR-655 by targeting membrane-associated guanylate kinase (*MAGI2*) induces gefitinib resistance (42). In chronic myelogenous leukemia (CML) both miR-17/92 cluster and tyrosine kinase activity were reported (125). Overexpression of receptor tyrosine kinases and miR-221/222 is reported in breast cancer. MET, EGF, and miR-3a/24-2 interaction are reported in non-small cell lung cancer (124). MiR-143/145 cluster is downregulated in KRAS mutant pancreatic cancer cells. Further, forced expression of this miRNA cluster inhibited tumorigenesis (126). Interestingly, the miR-143/145 cluster also targets *KRAS* and *RREB1* and is an inhibitor of Ras signaling (127). MiRNA clusters can promote EMT by targeting and inhibiting negative regulators of PI3K-AKT signaling. For example, miR-106b/25 (128), miR-23a/24-2 (129) and miR-17/106 (130) activate PI3K- AKT signaling by downregulation of *PTEN*. MiR-27a belonging to miR-23a/24-2 synergizes with AKT by targeting *FOXO1* (131). MiR-15/16 is a tumor suppressive cluster that inhibits prostate cancer cell invasion by suppressing the TGF-β signaling pathway (132). TGF-β and FGF-2 are reported to promote EMT in lung adenocarcinoma (PC-9 and HCC-827) cells through Smad3, MEK/extracellular-signal-regulated kinase (ERK), and mTOR pathways. Overexpression of miR-16 reduces the expression of fibroblast growth factor receptor 1 (*FGFR1*) and vascular endothelial growth factor receptor 2 (*VEGFR2*) in endothelial cells (133). MiR-143/145 is repressed by the activation of EGFR and Ras signaling (114). The miR-143 expression has been negatively correlated with EGFR in NSCLC cells. Transfection studies have shown that EGFR is a target of miR-143. MiR-99a/let-7/miR-125b is downregulated in malignant pleural mesothelioma (134, 135). MiRNA-99a targets (insulin-like growth factor 1 receptor) IGF1R/PI3K/AKT/mTOR and inhibits proliferation, migration, and invasion of cancer cells (136). Thus, altered expression of miRNAs can lead to inappropriate activation of tyrosine kinase pathways contributing to aggressiveness, progression and tumor resistant phenotypes in cancer cells via activation of EMT.

5.2. Integrin-linked kinase (ILK) pathway-integrin signaling

ILKs belong to Raf-like kinases (RAF) subfamily and are an intracellular serine/threonine kinase. It consisting of 5 ankyrin repeats, a phosphoinositide binding motif, and a kinase catalytic domain. ILKs act as a regulator of development and tissue homeostasis (137, 138). Being a downstream mediator of the Smad-TGF-β1 signaling pathway, the ILK pathway is implicated in EMT and the acquisition of invasive and metastatic phenotypes (138). ILKs interact with integrins and can be stimulated by growth factors and chemokines in a PI3K dependent manner. Overexpression of ILKs is reported in multiple cancers and inhibition of their activities could be used as a potential mechanism to control invasion and metastasis in cancer (139). ILKs are required for integrin-dependent focal adhesion. ILKs promote EMT via AKT1/GSK3β/CTNNB1 axis. Forced expression of ILK increased invasion and migration of cancer cells through nuclear translocation of CTNNB1 and downregulation of CDH1 (140). MiR-424/503 cluster expression is downregulated in SRC-transformed cells with its forced expression inhibiting cancer cell invasion (141). MiR-23b and miR-27b belonging to miR-23b/24-1 have also been downregulated during cSrc-induced transformed cells (142). MiRNAs have been reported to regulate the expression of specific integrins. The miR-17/92 cluster consists of 6 miRNA encoding genes namely miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a (143). MiR-92a is reported to suppress integrin α5 expression (144). In renal cell cancers, integrin α5 promotes metastasis (145). In ovarian cancer, the silencing of ILK upregulates miR-15a-miR-16-1 cluster (113). Integrin-α6β4 is a receptor for

laminin binding which promotes motility of cells in various types of cancer. In breast cancer, Integrin-α6β4 downregulates the expression of miR-25/32/92abc/363/363-3p/ 367 and miR-99ab/100 (146).

5.3. Ras pathway

Ras is a small GTP-binding protein that controls proliferation, differentiation, adhesion, apoptosis, and migration of cells in normal and pathological conditions (147). Overexpression of Ras signaling promotes growth, proliferation, migration, and invasion of cancer cells. Ras overexpression induces actin cytoskeleton remodeling, inhibits apoptosis and confers resistance to anticancer agents (147). Ras signaling induced EMT involves activation of MAPK, Hypoxia-Inducible Factor 1-Alpha (HIF1α) and PI3K/AKT/mTOR pathways, induction of *SANIL2*, *TWIST1*/2, *ZEB1*, and inhibition of *CDH1* (148). Activation of the RAS pathway is reported to regulate the expression of many miRNA clusters and vice versa (149). Ras initiates tumor-promoting pathways by repression of the miR-143/145 cluster (126). MiR-379/miR-656 is a downregulated miRNA cluster in glioblastoma (GBM) (127). Lassad *et al* 2015, showed an inverse correlation between expression of CYLD lysine 63 deubiquitinase (*CYLD*) and *KRAS* with the miR-183-96-182 cluster (150). The upregulation of AKT signaling is reported to induce EMT. MiR-154 and miR-37, belonging to DLK1-DIO3 microRNA mega-cluster, is elevated in prostate cancer, and it results in activation of E2F signaling, Ras pathway, hypoxia-inducible factor signaling, and the WNT and TGF-β pathways (151). MiR-144/451 inhibits esophageal cancer cell migration by downregulation of ERK/c-Myc signaling (152). Many previous studies have established the role of the Ras–MEK–ERK signaling pathway in EMT. The miR182 activates Ras–MEK–ERK signaling by suppressing RAS p21 protein activator 1 (*RASA1*) and sprouty-related EVH1 domain containing 1 (*SPRED1*) expression in squamous cell carcinoma of the oral cavity (153). KRAS overexpression induces NF-kB and inhibits *CDH1* expression via *SNAIL* and *MMP9* (154, 155). Ras-Raf-MEK1/2-ERK activates SLUG and represses *CDH1* expression (156). Ras-Ral-RAC family small GTPase (Rac), P21 activated kinases (PAK), Myosin light chain phosphatase (MLCP), Megalencephalic Leukoencephalopathy with Subcortical Cysts 1 (MLC) axis are implicated in focal adhesion formation contributing to EMT (157). MiR-23/24/27 cluster is downregulated in keratinocytes having HRas protooncogene (HrasG12 V) (158). MiR-17-92 regulation of Ras signaling is also reported (159). MiR-411 is a member of 4q32.31 miRNA cluster which promotes growth, proliferation, and metastasis in non-small-cell lung carcinoma (NSCLC) cell (160). miR-411-5p targets growth factor receptor bound protein 2 (GRB2)-son of sevenless homolog (SOS)-Ras signaling to prevent migration and invasion of breast cancer cells (161). Activation of the miR-221/222 cluster by Ras signaling is reported in basal-like breast cancer cells resulting in induction of EMT by downregulation Transcriptional Repressor GATA Binding 1 (TRPS1), a repressor of ZEB2 (115, 116).

5.4. Notch signaling pathway

Notch signaling is one of the highly conserved signaling pathways important for a cell to cell communication, cell differentiation, proliferation, invasion, migration, and apoptosis. Activation of Notch is reported to drive aberrant expression of EMT-TFs such as TWIST, SNAIL, SLUG, and ZEB1/2, with concomitant downregulation of CDH1 (162). Notch signaling activates genes associated with differentiation, survival, migration, invasion such as CCND1, c-Myc, and others. Notch crosstalk with EMT-TFs (SNAIL, SLUG) and growth factors (TGF-β, FGF, and PDGF) is implicated in EMT, chemoresistance, and metastasis (162). Overexpression of miR-200b inhibits Notch-1 expression (163, 164). Direct repression of the Delta/Notch pathway by miR-449 cluster controls vertebrate multiciliogenesis (165). Notch signaling can also activate oncogenic miRNA clusters. For instance, the activation of miR-17/92 in cancer by the Notch pathway leads to cellular proliferation. MiR-17/92 cluster promoter is predicted to poses a binding site for Hes family transcription factor 1 (*HES1*), an effector of Notch signaling. Moreover, B-Raf proto-oncogene (BRAFV600E) induces the expression of miR-17-92 via activation of Notch signaling (166). MiRNA-134 is a member of the delta-like non-canonical notch ligand -

iodothyronine deiodinase (DLK1-DIO3) cluster. MiRNA-134 is reported to regulate the expression of protein O-glucosyltransferase 1 (POGLUT1) and Notch pathway proteins in human endometrial cancers (167). Members of miR-206/miR-133b are reported to target NOTCH 3 in HeLa cells (168, 169).

5.5. Wnt signaling pathway

Activation of the canonical Wnt pathway, non-canonical planar cell polarity pathway, and non-canonical Wnt/calcium pathway is reported in various cancers. Many members of WNT signaling (WNTs, CTNNB1) either directly or indirectly activates SNAIL, SLUG, ZEB1/2, TWISTs, inhibit CDH1, and participate in the induction of EMT program (15, 170). MiRNA clusters are important for precise regulation of WNT signaling. Aberrant expression of miRNA clusters is reported to activate WNT signaling and to contribute to EMT. For example, transactivation of miR-371-373 by CTNNB1/ lymphoid enhancer binding factor 1 (LEF1) modulates Wnt/β-catenin-signaling pathways (171). MiR-30a/b/c/d/e-5p interaction with members of the canonical WNT pathway is reported to affect the treatment outcome in multiple myeloma (172). Crosstalk between PTEN/PI3K and Wnt pathway plays an important role in the subcellular localization of CTNNB1. Activation of the Wnt/β-catenin pathway and loss of *PTEN* activity is important for the initiation and progression of endometrial cancer (173). MiR-17/92 cluster by targeting PTEN/PI3K pathway promotes chemotherapeutic resistance and metastasis (174, 175). Metastasis suppressor protein 1 (*MTSS1*) is regulated by *PTEN* and is reported to inhibit EMT via inactivation of PI3K/AKT signaling (176). MiR-200a is an inhibitor of *CTNNB1*. MiR-145 is a tumor-suppressive miRNA belonging to the miR-143/miR-145 cluster. It targets catenin δ-1, disturbs the nuclear translocation of CTNNB1, and inhibits the transcription of c-Myc and *CCND1* (177).

5.6. Hedgehog signaling pathway

This pathway plays an important role in embryonic development, adult tissue maintenance, renewal, regeneration, differentiation, polarity, and proliferation. The defect in the hedgehog signaling pathway is reported in some cancers, especially during metastasis (178). It is a crucial regulator of EMT and is responsible for chemoresistance properties of human pancreatic Panc-1 cancer stem cells (179). Hedgehog (Hh) signaling participates in metastatic cascade by induction of EMT and angiogenesis (180). Hh signaling contributes to tumor development by inducing the expression of pro-tumorigenic genes such as *CCND1, ABCG2, BCL2, SNAIL, WNT2, VEGF* and *TGF-β* (181). In liver cancer, hedgehog enhances the expression of FAK/AKT, leading to increased secretion of MMP2 and MMP9 inducing EMT (182). Hedgehog via patched (*PTCH*) and glioma-associated oncogene (*GLI*) is reported to induce SNAIL expression and EMT (183). Human medulloblastoma shows constitutive activation of Sonic Hedgehog signaling and overexpression miR-17/92 cluster (184, 185). MiR-193b/365a cluster is downregulated in cutaneous squamous cell carcinomas (186). Hedgehog signaling activates its downstream target genes such as *BCL2, FOXC2,* Jagged 2 (*JAG2*), and *MYCN* via Smoothened (*SMO*) and *GLI* (187). MiR-193b is a transcriptional repressor of SMO. In colorectal cancer, hedgehog promotes EMT by activation of MMP2 and MMP9 via the induction of FAK and AKT. MiR-125b belonging to miR-99a/let-7c/miR-125b cluster expression is significantly low in ovarian, oral, cholangiocarcinoma and prostate cancer (188–191). MiR-125b has been reported to inhibit EMT by targeting hedgehog (192).

6. CONCLUSION

Taken together, miRNA clusters are a key regulator of the EMT process. Aberrant expression of miRNA contributes to the acquisition of various hallmarks of cancer including EMT. During metastasis, cancer cells adapt to permanently changing microenvironment and undergo transitions from differentiated to undifferentiated or partial EMTs (193). The partial or incomplete EMTs are activated by EMT-TFs. They increase the motility of cancer cells and favors metastasis and invasion. Apart from activation of EMT, EMT-TFs has several other

functions such as double-strand repair, senescence, pro-survival and anti-apoptotic phenotype under various types of stress conditions (194). Also, these EMT-TFs are tissue-specific, for example, SNAIL triggers metastasis in breast cancer with no effect being reported in pancreatic cancer (195). Therefore, further detailed studies are required to elucidate the role of miRNAs in partial EMT during cancer metastasis. With the involvement of miRNA clusters in various health and disease conditions, it is quite relevant to explore and understand the possibility of miRNA clusters in therapy as reviewed by Kabekkodu *et al*., 2018 (197). Unraveling miRNA regulation in EMT will make the mechanism more transparent and is likely to uncover novel biomarkers for different cancer types. Taken together, miRNA cluster and EMT-TF cross-talk coordinately regulate multiple members of pro-EMT signaling pathways and promotes EMT. Thus, inhibition of pro-EMT miRNA clusters or reactivation of anti-EMT miRNA clusters may be beneficial in controlling EMT and cancer metastasis.

7. ACKNOWLEDGMENTS

Vaibhav Shukla, Divya Adiga, and Jishnu Padacherri Vethil, contributed equally to this paper. We thank Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India (Grant No: EMR/2016/002314) and Department of Biotechnology (DBT), Government of India (6242-P8/RGCB/PMD/DBT/SPDK/2015, BT/PR2423/AGR/36/700/2011) for financial support. The authors acknowledge the support from TIFAC CORE in Pharmacogenomics, Government of India; DST-FIST, Government of India for infrastructure support, Manipal Academy of Higher Education (MAHE) for TMA Pai structured Ph.D. fellowships, and Senior Research Fellowship from Indian council for Medical Research (ICMR), Government of India.

8. REFERENCES

1. R Kalluri; RA Weinberg. The basics of epithelial-mesenchymal transition. J Clin Invest 119, 1420-8 (2009)
DOI: 10.1172/JCI39104

2. B Du; JS Shim. Targeting Epithelial-Mesenchymal Transition (EMT) to Overcome Drug Resistance in Cancer. Molecules 21, 965 (2016)
DOI: 10.3390/molecules21070965

3. DC Radisky. Epithelial-mesenchymal transition. J Cell Sci 118, 4325-4326 (2005)
DOI: 10.1242/jcs.02552

4. P Nisticò; MJ Bissell; DC Radisky. Epithelial-mesenchymal transition: General principles and pathological relevance with special emphasis on the role of matrix metalloproteinases. Cold Spring Harb Perspect Biol 4, a011908-a011908 (2012)
DOI: 10.1101/cshperspect.a011908

5. A Zaravinos. The Regulatory Role of MicroRNAs in EMT and Cancer. J Oncol 2015, 865816 (2015)
DOI: 10.1155/2015/865816

6. Y-S Kim; B-R Yi; N-H Kim; K-C Choi. Role of the epithelial-mesenchymal transition and its effects on embryonic stem cells. Exp Mol Med 46, e108 (2014)
DOI: 10.1038/emm.2014.44

7. J Lim; JP Thiery. Epithelial-mesenchymal transitions: insights from development. Development 139, 3471-86 (2012)
DOI: 10.1242/dev.071209

8. S Tojkander; G Gateva; P Lappalainen. Actin stress fibers--assembly, dynamics and biological roles. J Cell Sci 125, 1855-64 (2012)
DOI: 10.1242/jcs.098087

9. JP Thiery. Epithelial-mesenchymal transitions in tumour progression. Nat

Rev Cancer 2, 442-454 (2002)
DOI: 10.1038/nrc822

10. JP Thiery; H Acloque; RYJ Huang; MA Nieto. Epithelial-mesenchymal transitions in development and disease. Cell 139, 871-90 (2009)
DOI: 10.1016/j.cell.2009.11.007

11. A Legras; N Pécuchet; S Imbeaud; K Pallier; A Didelot; H Roussel; L Gibault; E Fabre; F Le Pimpec-Barthes; P Laurent-Puig; H Blons. Epithelial-to-Mesenchymal Transition and MicroRNAs in Lung Cancer. Cancers (Basel) 9, 101 (2017)
DOI: 10.3390/cancers9080101

12. JM Lee; S Dedhar; R Kalluri; EW Thompson. The epithelial-mesenchymal transition: new insights in signaling, development, and disease. J Cell Biol 172, 973-81 (2006)
DOI: 10.1083/jcb.200601018

13. MD Bullock; AE Sayan; GK Packham; AH Mirnezami. MicroRNAs: critical regulators of epithelial to mesenchymal (EMT) and mesenchymal to epithelial transition (MET) in cancer progression. Biol cell 104, 3-12 (2012)
DOI: 10.1111/boc.201100115

14. A Dongre; RA Weinberg. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 20, 69-84 (2019)
DOI: 10.1038/s41580-018-0080-4

15. DM Gonzalez; D Medici. Signaling mechanisms of the epithelial-mesenchymal transition. Sci Signal 7, re8 (2014)
DOI: 10.1126/scisignal.2005189

16. L YU; Y MU; N SA; H WANG; W XU. Tumor necrosis factor α induces epithelial-mesenchymal transition and promotes metastasis via NF-κB signaling pathway-mediated TWIST expression in hypopharyngeal cancer. Oncol Rep 31, 321-327 (2014)
DOI: 10.3892/or.2013.2841

17. Y-W Su; T-X Xie; D Sano; JN Myers. IL-6 Stabilizes Twist and Enhances Tumor Cell Motility in Head and Neck Cancer Cells through Activation of Casein Kinase 2. PLoS One 6, e19412 (2011)
DOI: 10.1371/journal.pone.0019412

18. CD Andl; T Mizushima; K Oyama; M Bowser; H Nakagawa; AK Rustgi. EGFR-induced cell migration is mediated predominantly by the JAK-STAT pathway in primary esophageal keratinocytes. Am J Physiol Gastrointest Liver Physiol 287, G1227-37 (2004)
DOI: 10.1152/ajpgi.00253.2004

19. H Zhong; K Chiles; D Feldser; E Laughner; C Hanrahan; MM Georgescu; JW Simons; GL Semenza. Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. Cancer Res 60, 1541-5 (2000)

20. JL Johnson; S Fenton; LG Sheffield. Prolactin inhibits epidermal growth factor-induced Ras-MAPK signaling in mammary epithelial cells. J Biol Chem 271, 21574-8 (1996)
DOI: 10.1074/jbc.271.35.21574

21. M Katz; I Amit; Y Yarden. Regulation of MAPKs by growth factors and receptor

tyrosine kinases. Biochim Biophys Acta 1773, 1161-76 (2007)
DOI: 10.1016/j.bbamcr.2007.01.002

22. M-H Yang; K-J Wu. TWIST activation by hypoxia inducible factor-1 (HIF-1): implications in metastasis and development. Cell Cycle 7, 2090-6 (2008)
DOI: 10.4161/cc.7.14.6324

23. MA Shields; S Dangi-Garimella; SB Krantz; DJ Bentrem; HG Munshi. Pancreatic cancer cells respond to type I collagen by inducing snail expression to promote membrane type 1 matrix metalloproteinase-dependent collagen invasion. J Biol Chem 286, 10495-504 (2011)
DOI: 10.1074/jbc.M110.195628

24. CP El-Haibi; GW Bell; J Zhang; AY Collmann; D Wood; CM Scherber; E Csizmadia; O Mariani; C Zhu; A Campagne; M Toner; SN Bhatia; D Irimia; A Vincent-Salomon; AE Karnoub. Critical role for lysyl oxidase in mesenchymal stem cell-driven breast cancer malignancy. Proc Natl Acad Sci U S A 109, 17460-5 (2012)
DOI: 10.1073/pnas.1206653109

25. W Tan; B Liu; S Qu; G Liang; W Luo; C Gong. MicroRNAs and cancer: Key paradigms in molecular therapy. Oncol Lett 15, 2735-2742 (2018)
DOI: 10.3892/ol.2017.7638

26. YS Lee; A Dutta. MicroRNAs in cancer. Annu Rev Pathol 4, 199-227 (2009)
DOI: 10.1146/annurev.pathol.4.1-10807.092222

27. L Cantini; G Bertoli; C Cava; T Dubois; A Zinovyev; M Caselle; I Castiglioni; E Barillot; L Martignetti. Identification of microRNA clusters cooperatively acting on epithelial to mesenchymal transition in triple negative breast cancer. Nucleic Acids Res 47, 2205-2215 (2019)
DOI: 10.1093/nar/gkz016

28. GG Jinesh; ER Flores; AS Brohl. Chromosome 19 miRNA cluster and CEBPB expression specifically mark and potentially drive triple negative breast cancers. PLoS One 13, e0206008 (2018)
DOI: 10.1371/journal.pone.0206008

29. B Liu; R Du; L Zhou; J Xu; S Chen; J Chen; X Yang; D Liu; Z Shao; L Zhang; Z Yu; N Xie; J Guan; S Liu. miR-200c/141 Regulates Breast Cancer Stem Cell Heterogeneity via Targeting HIPK1/β-Catenin Axis. Theranostics 8, 5801-5813 (2018)
DOI: 10.7150/thno.29380

30. B Li; Y Lu; L Yu; X Han; H Wang; J Mao; J Shen; B Wang; J Tang; C Li; B Song. miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/NF-κB/COX-2 activation. Chem Biol Interact 277, 33-42 (2017)
DOI: 10.1016/j.cbi.2017.08.014

31. Y Li; C Liang; H Ma; Q Zhao; Y Lu; Z Xiang; L Li; J Qin; Y Chen; WC Cho; RG Pestell; L Liang; Z Yu. miR-221/222 promotes S-phase entry and cellular migration in control of basal-like breast cancer. Molecules 19, 7122-37 (2014)
DOI: 10.3390/molecules19067122

32. Y-K Liang; H-Y Lin; X-W Dou; M Chen; X-L Wei; Y-Q Zhang; Y Wu; C-F Chen; J-W Bai; Y-S Xiao; Y-Z Qi; FAE Kruyt; G-J Zhang. MiR-221/222 promote epithelial-mesenchymal transition by targeting

Notch3 in breast cancer cell lines. NPJ breast cancer 4, 20 (2018)
DOI: 10.1038/s41523-018-0073-7

33. W Zhang; P Qian; X Zhang; M Zhang; H Wang; M Wu; X Kong; S Tan; K Ding; JK Perry; Z Wu; Y Cao; PE Lobie; T Zhu. Autocrine/Paracrine Human Growth Hormone-stimulated MicroRNA 96-182-183 Cluster Promotes Epithelial-Mesenchymal Transition and Invasion in Breast Cancer. J Biol Chem 290, 13812-29 (2015)
DOI: 10.1074/jbc.M115.653261

34. H Xia; LLPJ Ooi; KM Hui. MicroRNA-216a/217-induced epithelial-mesenchymal transition targets PTEN and SMAD7 to promote drug resistance and recurrence of liver cancer. Hepatology 58, 629-41 (2013)
DOI: 10.1002/hep.26369

35. F Liu; L Cheng; J Xu; F Guo; W Chen. miR-17-92 functions as an oncogene and modulates NF-κB signaling by targeting TRAF3 in MGC-803 human gastric cancer cells. Int J Oncol 53, 2241-2257 (2018)
DOI: 10.3892/ijo.2018.4543

36. W Jin; F Chen; K Wang; Y Song; X Fei; B Wu. miR-15a/miR-16 cluster inhibits invasion of prostate cancer cells by suppressing TGF-β signaling pathway. Biomed Pharmacother 104, 637-644 (2018)
DOI: 10.1016/j.biopha.2018.05.041

37. ST Kundu; LA Byers; DH Peng; JD Roybal; L Diao; J Wang; P Tong; CJ Creighton; DL Gibbons. The miR-200 family and the miR-183~96~182 cluster target Foxf2 to inhibit invasion and metastasis in lung cancers. Oncogene 35, 173-86 (2016)

38. Y Tian; Q Pan; Y Shang; R Zhu; J Ye; Y Liu; X Zhong; S Li; Y He; L Chen; J Zhao; W Chen; Z Peng; R Wang. MicroRNA-200 (miR-200) cluster regulation by achaete scute-like 2 (Ascl2): impact on the epithelial-mesenchymal transition in colon cancer cells. J Biol Chem 289, 36101-15 (2014)
DOI: 10.1074/jbc.M114.598383

39. R Ottman; J Levy; WE Grizzle; R Chakrabarti. The other face of miR-17-92a cluster, exhibiting tumor suppressor effects in prostate cancer. Oncotarget 7, 73739-73753 (2016)
DOI: 10.18632/oncotarget.12061

40. S Knoll; K Fürst; B Kowtharapu; U Schmitz; S Marquardt; O Wolkenhauer; H Martin; BM Pützer. E2F1 induces miR-224/452 expression to drive EMT through TXNIP downregulation. EMBO Rep 15, 1315-29 (2014)
DOI: 10.15252/embr.201439392

41. Y Zhou; Y Hu; M Yang; P Jat; K Li; Y Lombardo; D Xiong; RC Coombes; S Raguz; E Yagüe. The miR-106b~25 cluster promotes bypass of doxorubicin-induced senescence and increase in motility and invasion by targeting the E-cadherin transcriptional activator EP300. Cell Death Differ 21, 462-74 (2014)
DOI: 10.1038/cdd.2013.167

42. K Kitamura; M Seike; T Okano; K Matsuda; A Miyanaga; H Mizutani; R Noro; Y Minegishi; K Kubota; A Gemma. MiR-134/487b/655 cluster regulates TGF-β-induced epithelial-mesenchymal transition and drug resistance to gefitinib by targeting MAGI2 in lung adenocarcinoma cells. Mol Cancer Ther

13, 444-53 (2014)
DOI: 10.1158/1535-7163.MCT-13-0448

43. JL Attema; AG Bert; Y-Y Lim; N Kolesnikoff; DM Lawrence; KA Pillman; E Smith; PA Drew; Y Khew-Goodall; F Shannon; GJ Goodall. Identification of an enhancer that increases miR-200b~200a~429 gene expression in breast cancer cells. PLoS One 8, e75517 (2013)
DOI: 10.1371/journal.pone.0075517

44. AL Smith; R Iwanaga; DJ Drasin; DS Micalizzi; RL Vartuli; A-C Tan; HL Ford. The miR-106b-25 cluster targets Smad7, activates TGF-β signaling, and induces EMT and tumor initiating cell characteristics downstream of Six1 in human breast cancer. Oncogene 31, 5162-71 (2012)
DOI: 10.1038/onc.2012.11

45. Y Li; J Huo; X Pan; C Wang; X Ma. MicroRNA 302b-3p/302c-3p/302d-3p inhibits epithelial-mesenchymal transition and promotes apoptosis in human endometrial carcinoma cells. Onco Targets Ther Volume 11, 1275-1284 (2018)
DOI: 10.2147/OTT.S154517

46. H Maadi; A Moshtaghian; MF Taha; SJ Mowla; A Kazeroonian; NK Haass; A Javeri. Multimodal tumor suppression by miR-302 cluster in melanoma and colon cancer. Int J Biochem Cell Biol 81, 121-132 (2016)
DOI: 10.1016/j.biocel.2016.11.004

47. Z Wang; Y Li; D Kong; A Ahmad; S Banerjee; FH Sarkar. Cross-talk between miRNA and Notch signaling pathways in tumor development and progression. Cancer Lett 292, 141-148 (2010)
DOI: 10.1016/j.canlet.2009.11.012

48. J-L Zhao; L Zhang; X Guo; J-H Wang; W Zhou; M Liu; X Li; H Tang. miR-212/132 downregulates SMAD2 expression to suppress the G1/S phase transition of the cell cycle and the epithelial to mesenchymal transition in cervical cancer cells. IUBMB Life 67, 380-94 (2015)
DOI: 10.1002/iub.1381

49. XL Li; T Hara; Y Choi; M Subramanian; P Francis; S Bilke; RL Walker; M Pineda; Y Zhu; Y Yang; J Luo; LM Wakefield; T Brabletz; BH Park; S Sharma; D Chowdhury; PS Meltzer; A Lal. A p21-ZEB1 Complex Inhibits Epithelial-Mesenchymal Transition through the MicroRNA 183-96-182 Cluster. Mol Cell Biol 34, 533 (2014)
DOI: 10.1128/MCB.01043-13

50. M Korpal; ES Lee; G Hu; Y Kang. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. J Biol Chem 283, 14910-4 (2008)
DOI: 10.1074/jbc.C800074200

51. R Urbas; C Mayr; E Klieser; J Fuereder; D Bach; S Stättner; F Primavesi; T Jaeger; S Stanzer; AL Ress; M Löffelberger; A Wagner; F Berr; M Ritter; M Pichler; D Neureiter; T Kiesslich. Relevance of MicroRNA200 Family and MicroRNA205 for Epithelial to Mesenchymal Transition and Clinical Outcome in Biliary Tract Cancer Patients. Int J Mol Sci 17, 2053 (2016)
DOI: 10.3390/ijms17122053

52. E Casas; J Kim; A Bendesky; L Ohno-

Machado; CJ Wolfe; J Yang. Snail2 is an essential mediator of Twist1-induced epithelial mesenchymal transition and metastasis. Cancer Res 71, 245-54 (2011)
DOI: 10.1158/0008-5472.CAN-10-2330

53. Y Hu; M Dai; Y Zheng; J Wu; B Yu; H Zhang; W Kong; H Wu; X Yu. Epigenetic suppression of E-cadherin expression by Snail2 during the metastasis of colorectal cancer. Clin Epigenetics 10, 154 (2018)
DOI: 10.1186/s13148-018-0592-y

54. W Zhou; R Lv; W Qi; D Wu; Y Xu; W Liu; Y Mou; L Wang. Snail contributes to the maintenance of stem cell-like phenotype cells in human pancreatic cancer. PLoS One 9, e87409 (2014)
DOI: 10.1371/journal.pone.0087409

55. S Elloul; M Bukholt Elstrand; JM Nesland; CG Tropé; G Kvalheim; I Goldberg; R Reich; B Davidson. Snail, Slug, and Smad-interacting protein 1 as novel parameters of disease aggressiveness in metastatic ovarian and breast carcinoma. Cancer 103, 1631-1643 (2005)
DOI: 10.1002/cncr.20946

56. NK Kurrey; A K; SA Bapat. Snail and Slug are major determinants of ovarian cancer invasiveness at the transcription level. Gynecol Oncol 97, 155-65 (2005)
DOI: 10.1016/j.ygyno.2004.12.043

57. C Cobaleda; M Pérez-Caro; C Vicente-Dueñas; I Sánchez-García. Function of the Zinc-Finger Transcription Factor SNAI2 in Cancer and Development. Annu Rev Genet 41, 41-61 (2007)
DOI: 10.1146/annurev.genet.-41.110306.130146

58. Z-Q Wu; X-Y Li; CY Hu; M Ford; CG Kleer; SJ Weiss. Canonical Wnt signaling regulates Slug activity and links epithelial-mesenchymal transition with epigenetic Breast Cancer 1, Early Onset (BRCA1) repression. Proc Natl Acad Sci 109, 16654-16659 (2012)
DOI: 10.1073/pnas.1205822109

59. S Peiro; M Escrivà; I Puig; MJ Barberà; N Dave; N Herranz; MJ Larriba; M Takkunen; C Francí; A Muñoz; I Virtanen; J Baulida; AG de Herreros. Snail1 transcriptional repressor binds to its own promoter and controls its expression. Nucleic Acids Res 34, 2077-2084 (2006)
DOI: 10.1093/nar/gkl141

60. OM Martínez-Estrada; A Cullerés; FX Soriano; H Peinado; V Bolós; FO Martínez; M Reina; A Cano; M Fabre; S Vilaró. The transcription factors Slug and Snail act as repressors of Claudin-1 expression in epithelial cells. Biochem J 394, 449-57 (2006)
DOI: 10.1042/BJ20050591

61. HPH Naber; Y Drabsch; BE Snaar-Jagalska; P ten Dijke; T van Laar. Snail and Slug, key regulators of TGF-β-induced EMT, are sufficient for the induction of single-cell invasion. Biochem Biophys Res Commun 435, 58-63 (2013)
DOI: 10.1016/j.bbrc.2013.04.037

62. H Peinado; E Ballestar; M Esteller; A Cano. Snail mediates E-cadherin repression by the recruitment of the Sin3A/histone deacetylase 1 (HDAC1)/HDAC2 complex. Mol Cell Biol 24, 306-19 (2004)
DOI: 10.1128/MCB.24.1.306-319.2004

63. MA Smit; TR Geiger; J-Y Song; I

Gitelman; DS Peeper. A Twist-Snail Axis Critical for TrkB-Induced Epithelial-Mesenchymal Transition-Like Transformation, Anoikis Resistance, and Metastasis. Mol Cell Biol 29, 3722-3737 (2009)
DOI: 10.1128/MCB.01164-08

64. H Siemens; R Jackstadt; S Hünten; M Kaller; A Menssen; U Götz; H Hermeking. miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. Cell Cycle 10, 4256-4271 (2011)
DOI: 10.4161/cc.10.24.18552

65. S-M Park; AB Gaur; E Lengyel; ME Peter. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev 22, 894-907 (2008)
DOI: 10.1101/gad.1640608

66. Y ZHANG; X WANG; Z WANG; H TANG; H FAN; Q GUO. miR-182 promotes cell growth and invasion by targeting forkhead box F2 transcription factor in colorectal cancer. Oncol Rep 33, 2592-2598 (2015)
DOI: 10.3892/or.2015.3833

67. Y Qu; W-C Li; MR Hellem; K Rostad; M Popa; E McCormack; AM Oyan; K-H Kalland; X-S Ke. MiR-182 and miR-203 induce mesenchymal to epithelial transition and self-sufficiency of growth signals via repressing SNAI2 in prostate cells. Int J Cancer 133, 544-555 (2013)
DOI: 10.1002/ijc.28056

68. J Yu; J Li; Y Chen; W Cao; Y Lu; J Yang; E Xing. Snail Enhances Glycolysis in the Epithelial-Mesenchymal Transition Process by Targeting FBP1 in Gastric Cancer. Cell Physiol Biochem 43, 31-38 (2017)
DOI: 10.1159/000480314

69. W Li; C Liu; Y Tang; H Li; F Zhou; S Lv. Overexpression of Snail accelerates adriamycin induction of multidrug resistance in breast cancer cells. Asian Pac J Cancer Prev 12, 2575-80 (2011)

70. H Jin; Y Yu; T Zhang; X Zhou; J Zhou; L Jia; Y Wu; BP Zhou; Y Feng. Snail is critical for tumor growth and metastasis of ovarian carcinoma. Int J Cancer 126, n/a-n/a (2009)
DOI: 10.1002/ijc.24901

71. Y-C Wen; W-J Lee; P Tan; S-F Yang; M Hsiao; L-M Lee; M-H Chien. By inhibiting snail signaling and miR-23a-3p, osthole suppresses the EMT-mediated metastatic ability in prostate cancer. Oncotarget 6, 21120-36 (2015)
DOI: 10.18632/oncotarget.4229

72. J Li; X Xu; S Meng; Z Liang; X Wang; M Xu; S Wang; S Li; Y Zhu; B Xie; Y Lin; X Zheng; B Liu; L Xie. MET/SMAD3/SNAIL circuit mediated by miR-323a-3p is involved in regulating epithelial-mesenchymal transition progression in bladder cancer. Cell Death Dis 8, e3010 (2017)
DOI: 10.1038/cddis.2017.331

73. U Savita; D Karunagaran. MicroRNA-106b-25 cluster targets β-TRCP2, increases the expression of Snail and enhances cell migration and invasion in H1299 (non small cell lung cancer) cells. Biochem Biophys Res Commun 434, 841-847 (2013)
DOI: 10.1016/j.bbrc.2013.04.025

74. Q Chen; D Jiao; Y Wu; J Chen; J Wang;

X Tang; H Mou; H Hu; J Song; J Yan; L Wu; J Chen; Z Wang. MiR-206 inhibits HGF-induced epithelial-mesenchymal transition and angiogenesis in non-small cell lung cancer via c-Met /PI3k/Akt/mTOR pathway. Oncotarget 7, 18247-61 (2016)
DOI: 10.18632/oncotarget.7570

75. R Lei; J Tang; X Zhuang; R Deng; G Li; J Yu; Y Liang; J Xiao; H-Y Wang; Q Yang; G Hu. Suppression of MIM by microRNA-182 activates RhoA and promotes breast cancer metastasis. Oncogene 33, 1287-1296 (2014)
DOI: 10.1038/onc.2013.65

76. C Zhiping; T Shijun; W Linhui; W Yapei; Q Lianxi; D Qiang. MiR-181a promotes epithelial to mesenchymal transition of prostate cancer cells by targeting TGIF2. Eur Rev Med Pharmacol Sci 21, 4835-4843 (2017)

77. J-O Yoo; S-Y Kwak; H-J An; I-H Bae; M-J Park; Y-H Han. miR-181b-3p promotes epithelial-mesenchymal transition in breast cancer cells through Snail stabilization by directly targeting YWHAG. Biochim Biophys Acta - Mol Cell Res 1863, 1601-1611 (2016)
DOI: 10.1016/j.bbamcr.2016.04.016

78. Q Zhou; X Zheng; L Chen; B Xu; X Yang; J Jiang; C Wu. Smad2/3/4 Pathway Contributes to TGF-β-Induced MiRNA-181b Expression to Promote Gastric Cancer Metastasis by Targeting Timp3. Cell Physiol Biochem 39, 453-466 (2016)
DOI: 10.1159/000445638

79. N Zidar; E Boštjančič; M Jerala; N Kojc; D Drobne; B Štabuc; D Glavač. Down-regulation of microRNAs of the miR-200 family and up-regulation of Snail and Slug in inflammatory bowel diseases - hallmark of epithelial-mesenchymal transition. J Cell Mol Med 20, 1813-20 (2016)
DOI: 10.1111/jcmm.12869

80. D Jia; MK Jolly; SC Tripathi; P Den Hollander; B Huang; M Lu; M Celiktas; E Ramirez-Peña; E Ben-Jacob; JN Onuchic; SM Hanash; SA Mani; H Levine. Distinguishing mechanisms underlying EMT tristability. Cancer Converg 1, 2 (2017)
DOI: 10.1186/s41236-017-0005-8

81. R Rodriguez-Barrueco; EA Nekritz; F Bertucci; J Yu; F Sanchez-Garcia; TZ Zeleke; A Gorbatenko; D Birnbaum; E Ezhkova; C Cordon-Cardo; P Finetti; D Llobet-Navas; JM Silva. miR-424(322)/503 is a breast cancer tumor suppressor whose loss promotes resistance to chemotherapy. Genes Dev 31, 553-566 (2017)
DOI: 10.1101/gad.292318.116

82. H Zhang; J Tao; L Sheng; X Hu; R Rong; M Xu; T Zhu. Twist2 promotes kidney cancer cell proliferation and invasion by regulating ITGA6 and CD44 expression in the ECM-receptor interaction pathway. Onco Targets Ther 9, 1801 (2016)
DOI: 10.2147/OTT.S96535

83. ME Massari; C Murre. Helix-loop-helix proteins: regulators of transcription in eucaryotic organisms. Mol Cell Biol 20, 429-40 (2000)
DOI: 10.1128/MCB.20.2.429-440.2000

84. O Watanabe; H Imamura; T Shimizu; J Kinoshita; T Okabe; A Hirano; K Yoshimatsu; S Konno; M Aiba; K Ogawa. Expression of twist and wnt in human breast cancer. Anticancer Res 24, 3851-6

85. J Dupont; AM Fernandez; CA Glackin; L Helman; D LeRoith. Insulin-like Growth Factor 1 (IGF-1)-induced Twist Expression Is Involved in the Anti-apoptotic Effects of the IGF-1 Receptor. J Biol Chem 276, 26699-26707 (2001)
DOI: 10.1074/jbc.M102664200

86. H-W Lo; S-C Hsu; W Xia; X Cao; J-Y Shih; Y Wei; JL Abbruzzese; GN Hortobagyi; M-C Hung. Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression. Cancer Res 67, 9066-76 (2007)
DOI: 10.1158/0008-5472.CAN-07-0575

87. Q Zheng; S Diao; Q Wang; C Zhu; X Sun; B Yin; X Zhang; X Meng; B Wang. IL-17A promotes cell migration and invasion of glioblastoma cells via activation of PI3K/AKT signalling pathway. J Cell Mol Med 23, 357 (2019)
DOI: 10.1111/jcmm.13938

88. M-H Yang; M-Z Wu; S-H Chiou; P-M Chen; S-Y Chang; C-J Liu; S-C Teng; K-J Wu. Direct regulation of TWIST by HIF-1α promotes metastasis. Nat Cell Biol 10, 295-305 (2008)
DOI: 10.1038/ncb1691

89. T Wang; J Hou; Z Li; Z Zheng; J Wei; D Song; T Hu; Q Wu; JY Yang; J-C Cai. miR-15a-3p and miR-16-1-3p Negatively Regulate Twist1 to Repress Gastric Cancer Cell Invasion and Metastasis. Int J Biol Sci 13, 122-134 (2017)
DOI: 10.7150/ijbs.14770

90. Y-B Lee; I Bantounas; D-Y Lee; L Phylactou; MA Caldwell; JB Uney. Twist-1 regulates the miR-199a/214 cluster during development. Nucleic Acids Res 37, 123-128 (2009)
DOI: 10.1093/nar/gkn920

91. D Chen; B-L Dang; J Huang; M Chen; D Wu; M-L Xu; R Li; G-R Yan. MiR-373 drives the epithelial-to-mesenchymal transition and metastasis via the miR-373-TXNIP-HIF1α-TWIST signaling axis in breast cancer. Oncotarget 6, 32701-12 (2015)
DOI: 10.18632/oncotarget.4702

92. B-F Chen; Y-K Suen; S Gu; L Li; W-Y Chan. A miR-199a/miR-214 self-regulatory network via PSMD10, TP53 and DNMT1 in testicular germ cell tumor. Sci Rep 4, 6413 (2014)
DOI: 10.1038/srep06413

93. G Yin; R Chen; AB Alvero; H-H Fu; J Holmberg; C Glackin; T Rutherford; G Mor. TWISTing stemness, inflammation and proliferation of epithelial ovarian cancer cells through MIR199A2/214. Oncogene 29, 3545-3553 (2010)
DOI: 10.1038/onc.2010.111

94. DJ Drasin; AL Guarnieri; D Neelakantan; J Kim; JH Cabrera; C-A Wang; V Zaberezhnyy; P Gasparini; L Cascione; K Huebner; A-C Tan; HL Ford. TWIST1-Induced miR-424 Reversibly Drives Mesenchymal Programming while Inhibiting Tumor Initiation. Cancer Res 75, 1908-1921 (2015)
DOI: 10.1158/0008-5472.CAN-14-2394

95. WL Yau; CSC Lam; L Ng; AKM Chow; STC Chan; JYK Chan; JYH Wo; KTP Ng; K Man; RTP Poon; RWC Pang. Over-Expression of miR-106b Promotes Cell Migration and Metastasis in

Hepatocellular Carcinoma by Activating Epithelial-Mesenchymal Transition Process. PLoS One 8, e57882 (2013)
DOI: 10.1371/journal.pone.0057882

96. M Liu; L Liu; M Bai; L Zhang; F Ma; X Yang; S Sun. Hypoxia-induced activation of Twist/miR-214/E-cadherin axis promotes renal tubular epithelial cell mesenchymal transition and renal fibrosis. Biochem Biophys Res Commun 495, 2324-2330 (2018)
DOI: 10.1016/j.bbrc.2017.12.130

97. PNN Nguyen; KB Choo; C-J Huang; S Sugii; SK Cheong; T Kamarul. miR-524-5p of the primate-specific C19MC miRNA cluster targets TP53IPN1- and EMT-associated genes to regulate cellular reprogramming. Stem Cell Res Ther 8, 214 (2017)
DOI: 10.1186/s13287-017-0666-3

98. ML Abba; N Patil; JH Leupold; H Allgayer. MicroRNA Regulation of Epithelial to Mesenchymal Transition. J Clin Med 5 (2016)
DOI: 10.3390/jcm5010008

99. S TAMAGAWA; LB BEDER; M HOTOMI; M GUNDUZ; K YATA; R GRENMAN; N YAMANAKA. Role of miR-200c/miR-141 in the regulation of epithelial-mesenchymal transition and migration in head and neck squamous cell carcinoma. Int J Mol Med 33, 879-886 (2014)
DOI: 10.3892/ijmm.2014.1625

100. D Senfter; S Holzner; M Kalipciyan; A Staribacher; A Walzl; N Huttary; S Krieger; S Brenner; W Jager; G Krupitza; H Dolznig; RM Mader. Loss of miR-200 family in 5-fluorouracil resistant colon cancer drives lymphendothelial invasiveness *in vitro*. Hum Mol Genet 24, 3689-98 (2015)
DOI: 10.1093/hmg/ddv113

101. S Sass; S Dietmann; U Burk; S Brabletz; D Lutter; A Kowarsch; KF Mayer; T Brabletz; A Ruepp; F Theis; Y Wang. MicroRNAs coordinately regulate protein complexes. BMC Syst Biol 5, 136 (2011)
DOI: 10.1186/1752-0509-5-136

102. S Rachagani; MA Macha; N Heimann; P Seshacharyulu; D Haridas; S Chugh; SK Batra. Clinical implications of miRNAs in the pathogenesis, diagnosis and therapy of pancreatic cancer. Adv Drug Deliv Rev 81, 16-33 (2015)
DOI: 10.1016/j.addr.2014.10.020

103. J You; Y Li; N Fang; B Liu; L Zu; R Chang; X Li; Q Zhou. MiR-132 Suppresses the Migration and Invasion of Lung Cancer Cells via Targeting the EMT Regulator ZEB2. PLoS One 9, e91827 (2014)
DOI: 10.1371/journal.pone.0091827

104. B Ell; Q Qiu; Y Wei; L Mercatali; T Ibrahim; D Amadori; Y Kang. The MicroRNA-23b/27b/24 Cluster Promotes Breast Cancer Lung Metastasis by Targeting Metastasis-suppressive Gene Prosaposin. J Biol Chem 289, 21888-21895 (2014)
DOI: 10.1074/jbc.M114.582866

105. J Cao; J Liu; J Long; J Fu; L Huang; J Li; C Liu; X Zhang; Y Yan. microRNA-23b suppresses epithelial-mesenchymal transition (EMT) and metastasis in hepatocellular carcinoma via targeting Pyk2. Biomed Pharmacother 89, 642-650 (2017)
DOI: 10.1016/j.biopha.2017.02.030

106. S Majid; AA Dar; S Saini; G Deng; I Chang; K Greene; Y Tanaka; R Dahiya;

S Yamamura. MicroRNA-23b Functions as a Tumor Suppressor by Regulating Zeb1 in Bladder Cancer. PLoS One 8, e67686 (2013)
DOI: 10.1371/journal.pone.0067686

107. PA Gregory; CP Bracken; E Smith; AG Bert; JA Wright; S Roslan; M Morris; L Wyatt; G Farshid; Y-Y Lim; GJ Lindeman; MF Shannon; PA Drew; Y Khew-Goodall; GJ Goodall. An autocrine TGF-beta/ZEB/miR-200 signaling network regulates establishment and maintenance of epithelial-mesenchymal transition. Mol Biol Cell 22, 1686-98 (2011)
DOI: 10.1091/mbc.e11-02-0103

108. L Romero-Pérez; MÁ López-García; J Díaz-Martín; M Biscuola; MÁ Castilla; LJ Tafe; K Garg; E Oliva; X Matias-Guiu; RA Soslow; J Palacios. ZEB1 overexpression associated with E-cadherin and microRNA-200 downregulation is characteristic of undifferentiated endometrial carcinoma. Mod Pathol 26, 1514-1524 (2013)
DOI: 10.1038/modpathol.2013.93

109. Y Yanaka; T Muramatsu; H Uetake; K Kozaki; J Inazawa. miR-544a induces epithelial-mesenchymal transition through the activation of WNT signaling pathway in gastric cancer. Carcinogenesis 36, 1363-1371 (2015)
DOI: 10.1093/carcin/bgv106

110. G Di Leva; P Gasparini; C Piovan; A Ngankeu; M Garofalo; C Taccioli; M V. Iorio; M Li; S Volinia; H Alder; T Nakamura; G Nuovo; Y Liu; KP Nephew; CM Croce. MicroRNA Cluster 221-222 and Estrogen Receptor α Interactions in Breast Cancer. JNCI J Natl Cancer Inst 102, 706-721 (2010)
DOI: 10.1093/jnci/djq102

111. X Yan; X Chen; H Liang; T Deng; W Chen; S Zhang; M Liu; X Gao; Y Liu; C Zhao; X Wang; N Wang; J Li; R Liu; K Zen; C-Y Zhang; B Liu; Y Ba. miR-143 and miR-145 synergistically regulate ERBB3 to suppress cell proliferation and invasion in breast cancer. Mol Cancer 13, 220 (2014)
DOI: 10.1186/1476-4598-13-220

112. JN Psathas; PJ Doonan; P Raman; BD Freedman; AJ Minn; A Thomas-Tikhonenko. The Myc-miR-17-92 axis amplifies B-cell receptor signaling via inhibition of ITIM proteins: a novel lymphomagenic feed-forward loop. Blood 122, 4220-9 (2013)
DOI: 10.1182/blood-2012-12-473090

113. D Yuan; Y Zhao; Y Wang; J Che; W Tan; Y Jin; F Wang; P Li; S Fu; Q Liu; W Zhu. Effect of integrin-linked kinase gene silencing on microRNA expression in ovarian cancer. Mol Med Rep 16, 7267-7276 (2017)
DOI: 10.3892/mmr.2017.7523

114. S Wang; JC Liu; Y Ju; G Pellecchia; V Voisin; D-Y Wang; R Leha L; Y Ben-David; GD Bader; E Zacksenhaus. microRNA-143/145 loss induces Ras signaling to promote aggressive Pten-deficient basal-like breast cancer. JCI insight 2 (2017)
DOI: 10.1172/jci.insight.93313

115. EN Howe; DR Cochrane; JK Richer. The miR-200 and miR-221/222 microRNA families: opposing effects on epithelial identity. J Mammary Gland Biol Neoplasia 17, 65-77 (2012)
DOI: 10.1007/s10911-012-9244-6

116. S Stinson; MR Lackner; AT Adai; N Yu; H-J Kim; C O'Brien; J Spoerke; S Jhunjhunwala; Z Boyd; T Januario; RJ Newman; P Yue; R Bourgon; Z Modrusan; HM Stern; S Warming; FJ de Sauvage; L Amler; R-F Yeh; D Dornan. TRPS1 targeting by miR-221/222 promotes the epithelial-to-mesenchymal transition in breast cancer. Sci Signal 4, ra41 (2011)
DOI: 10.1126/scisignal.2001538

117. AL Guarnieri; CG Towers; DJ Drasin; MUJ Oliphant; Z Andrysik; TJ Hotz; RL Vartuli; ES Linklater; A Pandey; S Khanal; JM Espinosa; HL Ford. The miR-106b-25 cluster mediates breast tumor initiation through activation of NOTCH1 via direct repression of NEDD4L. Oncogene 37, 3879-3893 (2018)
DOI: 10.1038/s41388-018-0239-7

118. S Brabletz; K Bajdak; S Meidhof; U Burk; G Niedermann; E Firat; U Wellner; A Dimmler; G Faller; J Schubert; T Brabletz. The ZEB1/miR-200 feedback loop controls Notch signalling in cancer cells. EMBO J 30, 770-782 (2011)
DOI: 10.1038/emboj.2010.349

119. A Guinot; F Oeztuerk-Winder; J-J Ventura. miR-17-92/p38α Dysregulation Enhances Wnt Signaling and Selects Lgr6 + Cancer Stem-like Cells during Lung Adenocarcinoma Progression. Cancer Res 76, 4012-4022 (2016)
DOI: 10.1158/0008-5472.CAN-15-3302

120. M Preusse; FJ Theis; NS Mueller. miTALOS v2: Analyzing Tissue Specific microRNA Function. PLoS One 11, e0151771 (2016)
DOI: 10.1371/journal.pone.0151771

121. PA Northcott; A Fernandez-L; JP Hagan; DW Ellison; W Grajkowska; Y Gillespie; R Grundy; T Van Meter; JT Rutka; CM Croce; AM Kenney; MD Taylor. The miR-17/92 polycistron is up-regulated in sonic hedgehog-driven medulloblastomas and induced by N-myc in sonic hedgehog-treated cerebellar neural precursors. Cancer Res 69, 3249-55 (2009)
DOI: 10.1158/0008-5472.CAN-08-4710

122. E Li; K Hristova. Role of receptor tyrosine kinase transmembrane domains in cell signaling and human pathologies. Biochemistry 45, 6241-51 (2006)
DOI: 10.1021/bi060609y

123. K Sekhon; N Bucay; S Majid; R Dahiya; S Saini. MicroRNAs and epithelial-mesenchymal transition in prostate cancer. Oncotarget 7, 67597-67611 (2016)
DOI: 10.18632/oncotarget.11708

124. M Acunzo; G Romano; D Palmieri; A Laganá; M Garofalo; V Balatti; A Drusco; M Chiariello; P Nana-Sinkam; CM Croce. Cross-talk between MET and EGFR in non-small cell lung cancer involves miR-27a and Sprouty2. Proc Natl Acad Sci U S A 110, 8573-8 (2013)
DOI: 10.1073/pnas.1302107110

125. L Venturini; K Battmer; M Castoldi; B Schultheis; A Hochhaus; MU Muckenthaler; A Ganser; M Eder; M Scherr. Expression of the miR-17-92 polycistron in chronic myeloid leukemia (CML) CD34+ cells. Blood 109, 4399-405 (2007)
DOI: 10.1182/blood-2006-09-045104

126. OA Kent; RR Chivukula; M Mullendore; EA Wentzel; G Feldmann; KH Lee; S Liu; SD Leach; A Maitra; JT Mendell. Repression of the miR-143/145 cluster by

oncogenic Ras initiates a tumor-promoting feed-forward pathway. Genes Dev 24, 2754-9 (2010)
DOI: 10.1101/gad.1950610

127. OA Kent; K Fox-Talbot; MK Halushka. RREB1 repressed miR-143/145 modulates KRAS signaling through downregulation of multiple targets. Oncogene 32, 2576-85 (2013)
DOI: 10.1038/onc.2012.266

128. L Poliseno; L Salmena; L Riccardi; A Fornari; MS Song; RM Hobbs; P Sportoletti; S Varmeh; A Egia; G Fedele; L Rameh; M Loda; PP Pandolfi. Identification of the miR-106b~25 microRNA cluster as a proto-oncogenic PTEN-targeting intron that cooperates with its host gene MCM7 in transformation. Sci Signal 3, ra29 (2010)
DOI: 10.1126/scisignal.2000594

129. JL Kurkewich; J Hansen; N Klopfenstein; H Zhang; C Wood; A Boucher; J Hickman; DE Muench; HL Grimes; R Dahl. The miR-23a~27a~24-2 microRNA cluster buffers transcription and signaling pathways during hematopoiesis. PLoS Genet 13, e1006887 (2017)
DOI: 10.1371/journal.pgen.1006887

130. H Naka-Kaneda; S Nakamura; M Igarashi; H Aoi; H Kanki; J Tsuyama; S Tsutsumi; H Aburatani; T Shimazaki; H Okano. The miR-17/106-p38 axis is a key regulator of the neurogenic-to-gliogenic transition in developing neural stem/progenitor cells. Proc Natl Acad Sci U S A 111, 1604-9 (2014)
DOI: 10.1073/pnas.1315567111

131. IK Guttilla; BA White. Coordinate regulation of FOXO1 by miR-27a, miR-96, and miR-182 in breast cancer cells. J Biol Chem 284, 23204-16 (2009)
DOI: 10.1074/jbc.M109.031427

132. D Bonci; V Coppola; M Patrizii; A Addario; A Cannistraci; F Francescangeli; R Pecci; G Muto; D Collura; R Bedini; A Zeuner; M Valtieri; S Sentinelli; MS Benassi; M Gallucci; P Carlini; S Piccolo; R De Maria. A microRNA code for prostate cancer metastasis. Oncogene 35, 1180-92 (2016)
DOI: 10.1038/onc.2015.176

133. A Chamorro-Jorganes; E Araldi; LOF Penalva; D Sandhu; C Fernández-Hernando; Y Suárez. MicroRNA-16 and MicroRNA-424 regulate cell-autonomous angiogenic functions in endothelial cells via targeting vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1. Arterioscler Thromb Vasc Biol 31, 2595-2606 (2011)
DOI: 10.1161/ATVBAHA.111.236521

134. H-B Zhang; L-C Sun; L Ling; L-H Cong; R Lian. miR-143 suppresses the proliferation of NSCLC cells by inhibiting the epidermal growth factor receptor. Exp Ther Med 12, 1795-1802 (2016)
DOI: 10.3892/etm.2016.3555

135. A Truini; S Coco; E Nadal; C Genova; M Mora; MG Dal Bello; I Vanni; A Alama; E Rijavec; F Biello; G Barletta; DF Merlo; A Valentino; P Ferro; GL Ravetti; S Stigliani; A Vigani; F Fedeli; DG Beer; S Roncella; F Grossi. Downregulation of miR-99a/let-7c/miR-125b miRNA cluster predicts clinical outcome in patients with unresected malignant pleural mesothelioma. Oncotarget 8, 68627-68640 (2017)
DOI: 10.18632/oncotarget.19800

136. Y Jin; SD Tymen; D Chen; ZJ Fang; Y Zhao; D Dragas; Y Dai; PT Marucha; X Zhou. MicroRNA-99 family targets AKT/mTOR signaling pathway in dermal wound healing. PLoS One 8, e64434 (2013)
DOI: 10.1371/journal.pone.0064434

137. D Gil; D Ciołczyk-Wierzbicka; J Dulińska-Litewka; K Zwawa; JA McCubrey; P Laidler. The mechanism of contribution of integrin linked kinase (ILK) to epithelial-mesenchymal transition (EMT). Adv Enzyme Regul 51, 195-207 (2011)
DOI: 10.1016/j.advenzreg.2010.09.005

138. I Serrano; PC McDonald; FE Lock; S Dedhar. Role of the integrin-linked kinase (ILK)/Rictor complex in TGFβ-1-induced epithelial-mesenchymal transition (EMT). Oncogene 32, 50-60 (2013)
DOI: 10.1038/onc.2012.30

139. LA Shirley; S McCarty; M-C Yang; M Saji; X Zhang; J Phay; MD Ringel; C-S Chen. Integrin-linked kinase affects signaling pathways and migration in thyroid cancer cells and is a potential therapeutic target. Surgery 159, 163-70 (2016)
DOI: 10.1016/j.surg.2015.10.016

140. A Oloumi; T McPhee; S Dedhar. Regulation of E-cadherin expression and beta-catenin/Tcf transcriptional activity by the integrin-linked kinase. Biochim Biophys Acta 1691, 1-15 (2004)
DOI: 10.1016/j.bbamcr.2003.12.002

141. C Oneyama; Y Kito; R Asai; J Ikeda; T Yoshida; D Okuzaki; R Kokuda; K Kakumoto; K Takayama; S Inoue; E Morii; M Okada. MiR-424/503-mediated Rictor upregulation promotes tumor progression. PLoS One 8, e80300 (2013)
DOI: 10.1371/journal.pone.0080300

142. C Oneyama; M Okada. MicroRNAs as the fine-tuners of Src oncogenic signalling. J Biochem 157, 431-8 (2015)
DOI: 10.1093/jb/mvv036

143. L-L Fang; X-H Wang; B-F Sun; X-D Zhang; X-H Zhu; Z-J Yu; H Luo. Expression, regulation and mechanism of action of the miR-17-92 cluster in tumor cells (Review). Int J Mol Med 40, 1624-1630 (2017)
DOI: 10.3892/ijmm.2017.3164

144. C Ohyagi-Hara; K Sawada; S Kamiura; Y Tomita; A Isobe; K Hashimoto; Y Kinose; S Mabuchi; T Hisamatsu; T Takahashi; K Kumasawa; S Nagata; K-I Morishige; E Lengyel; H Kurachi; T Kimura. miR-92a inhibits peritoneal dissemination of ovarian cancer cells by inhibiting integrin α5 expression. Am J Pathol 182, 1876-89 (2013)
DOI: 10.1016/j.ajpath.2013.01.039

145. I Breuksch; F Prosinger; F Baehr; F-P Engelhardt; H-K Bauer; JW Thüroff; A-S Heimes; A Hasenburg; D Prawitt; W Brenner. Integrin α5 triggers the metastatic potential in renal cell carcinoma. Oncotarget 8 (2017)
DOI: 10.18632/oncotarget.22501

146. KD Gerson; VSRK Maddula; BE Seligmann; JR Shearstone; A Khan; AM Mercurio. Effects of β4 integrin expression on microRNA patterns in breast cancer. Biol Open 1, 658-66 (2012)
DOI: 10.1242/bio.20121628

147. A Fernández-Medarde; E Santos. Ras in cancer and developmental diseases. Genes Cancer 2, 344-58 (2011)

DOI: 10.1177/1947601911411084

148. YA Fouad; C Aanei. Revisiting the hallmarks of cancer. Am J Cancer Res 7, 1016-1036 (2017)

149. J Masliah-Planchon; S Garinet; E Pasmant. RAS-MAPK pathway epigenetic activation in cancer: miRNAs in action. Oncotarget 7, 38892-38907 (2016)
DOI: 10.18632/oncotarget.6476

150. L Oussaief; A Fendri; B Chane-Woon-Ming; R Poirey; H-J Delecluse; I Joab; S Pfeffer. Modulation of MicroRNA Cluster miR-183-96-182 Expression by Epstein-Barr Virus Latent Membrane Protein 1. J Virol 89, 12178-88 (2015)
DOI: 10.1128/JVI.01757-15

151. M Gururajan; S Josson; GC-Y Chu; C-L Lu; Y-T Lu; CL Haga; HE Zhau; C Liu; J Lichterman; P Duan; EM Posadas; LWK Chung. miR-154* and miR-379 in the DLK1-DIO3 microRNA mega-cluster regulate epithelial to mesenchymal transition and bone metastasis of prostate cancer. Clin Cancer Res 20, 6559-69 (2014)
DOI: 10.1158/1078-0432.CCR-14-1784

152. Z Gao; P Zhang; M Xie; H Gao; L Yin; R Liu. miR-144/451 cluster plays an oncogenic role in esophageal cancer by inhibiting cell invasion. Cancer Cell Int 18, 184 (2018)
DOI: 10.1186/s12935-018-0679-8

153. J Wang; W Wang; J Li; L Wu; M Song; Q Meng. miR182 activates the Ras-MEK-ERK pathway in human oral cavity squamous cell carcinoma by suppressing RASA1 and SPRED1. Onco Targets Ther 10, 667-679 (2017)
DOI: 10.2147/OTT.S121864

154. J Ling; Y Kang; R Zhao; Q Xia; D-F Lee; Z Chang; J Li; B Peng; JB Fleming; H Wang; J Liu; IR Lemischka; M-C Hung; PJ Chiao. KrasG12D-induced IKK2/β/NF-κB activation by IL-1α and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell 21, 105-20 (2012)
DOI: 10.1016/j.ccr.2011.12.006

155. CR Schmidt; YJ Gi; TA Patel; RJ Coffey; RD Beauchamp; AS Pearson. E-cadherin is regulated by the transcriptional repressor SLUG during Ras-mediated transformation of intestinal epithelial cells. Surgery 138, 306-12 (2005)
DOI: 10.1016/j.surg.2005.06.007

156. JA McCubrey; LS Steelman; WH Chappell; SL Abrams; G Montalto; M Cervello; F Nicoletti; P Fagone; G Malaponte; MC Mazzarino; S Candido; M Libra; J Bäsecke; S Mijatovic; D Maksimovic-Ivanic; M Milella; A Tafuri; L Cocco; C Evangelisti; F Chiarini; AM Martelli. Mutations and deregulation of Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR cascades which alter therapy response. Oncotarget 3, 954-87 (2012)
DOI: 10.18632/oncotarget.652

157. MC Gutjahr; J Rossy; V Niggli. Role of Rho, Rac, and Rho-kinase in phosphorylation of myosin light chain, development of polarity, and spontaneous migration of Walker 256 carcinosarcoma cells. Exp Cell Res 308, 422-38 (2005)
DOI: 10.1016/j.yexcr.2005.05.001

158. K Riemondy; X Wang; EC Torchia; DR

Roop; R Yi. MicroRNA-203 represses selection and expansion of oncogenic Hras transformed tumor initiating cells. Elife 4 (2015)
DOI: 10.7554/eLife.07004

159. L Hong; M Lai; M Chen; C Xie; R Liao; YJ Kang; C Xiao; W-Y Hu; J Han; P Sun. The miR-17-92 cluster of microRNAs confers tumorigenicity by inhibiting oncogene-induced senescence. Cancer Res 70, 8547-57 (2010)
DOI: 10.1158/0008-5472.CAN-10-1938

160. C Zhang; H Wang; X Liu; Y Hu; L Ding; X Zhang; Q Sun; Y Li. Oncogenic microRNA-411 promotes lung carcinogenesis by directly targeting suppressor genes SPRY4 and TXNIP. Oncogene 38, 1892-1904 (2019)
DOI: 10.1038/s41388-018-0534-3

161. Y Zhang; G Xu; G Liu; Y Ye; C Zhang; C Fan; H Wang; H Cai; R Xiao; Z Huang; Q Luo. miR-411-5p inhibits proliferation and metastasis of breast cancer cell via targeting GRB2. Biochem Biophys Res Commun 476, 607-613 (2016)
DOI: 10.1016/j.bbrc.2016.06.006

162. Z Wang; Y Li; D Kong; FH Sarkar. The role of Notch signaling pathway in epithelial-mesenchymal transition (EMT) during development and tumor aggressiveness. Curr Drug Targets 11, 745-51 (2010)
DOI: 10.2174/138945010791170860

163. X Yang; W Ni; K Lei. miR-200b suppresses cell growth, migration and invasion by targeting Notch1 in nasopharyngeal carcinoma. Cell Physiol Biochem 32, 1288-98 (2013)
DOI: 10.1159/000354527

164. F Ning; Q Zhou; X Chen. miR-200b promotes cell proliferation and invasion in t-cell acute Lymphoblastic leukemia through NOTCH1. J Biol Regul Homeost Agents 32, 1467-1471

165. B Marcet; B Chevalier; G Luxardi; C Coraux; L-E Zaragosi; M Cibois; K Robbe-Sermesant; T Jolly; B Cardinaud; C Moreilhon; L Giovannini-Chami; B Nawrocki-Raby; P Birembaut; R Waldmann; L Kodjabachian; P Barbry. Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway. Nat Cell Biol 13, 693-9 (2011)
DOI: 10.1038/ncb2241

166. CS Fuziwara; ET Kimura. Insights into Regulation of the miR-17-92 Cluster of miRNAs in Cancer. Front Med 2, 64 (2015)
DOI: 10.3389/fmed.2015.00064

167. Y Gao; T Liu; Y Huang. MicroRNA-134 suppresses endometrial cancer stem cells by targeting POGLUT1 and Notch pathway proteins. FEBS Lett 589, 207-14 (2015)
DOI: 10.1016/j.febslet.2014.12.002

168. G Song; Y Zhang; L Wang. MicroRNA-206 targets notch3, activates apoptosis, and inhibits tumor cell migration and focus formation. J Biol Chem 284, 31921-7 (2009)
DOI: 10.1074/jbc.M109.046862

169. N Nohata; T Hanazawa; H Enokida; N Seki. microRNA-1/133a and microRNA-206/133b clusters: dysregulation and functional roles in human cancers. Oncotarget 3, 9-21 (2012)
DOI: 10.18632/oncotarget.424

170. S Basu; S Cheriyamundath; A Ben-Ze'ev. Cell-cell adhesion: linking Wnt/β-catenin signaling with partial EMT and stemness traits in tumorigenesis. F1000Research 7, 1488 (2018)
DOI: 10.12688/f1000research.15782.1

171. A-D Zhou; L-T Diao; H Xu; Z-D Xiao; J-H Li; H Zhou; L-H Qu. β-Catenin/LEF1 transactivates the microRNA-371-373 cluster that modulates the Wnt/β-catenin-signaling pathway. Oncogene 31, 2968-78 (2012)
DOI: 10.1038/onc.2011.461

172. J-J Zhao; RD Carrasco. Crosstalk between microRNA30a/b/c/d/e-5p and the canonical Wnt pathway: implications for multiple myeloma therapy. Cancer Res 74, 5351-8 (2014)
DOI: 10.1158/0008-5472.CAN-14-0994

173. M van der Zee; Y Jia; Y Wang; C Heijmans-Antonissen; PC Ewing; P Franken; FJ DeMayo; JP Lydon; CW Burger; R Fodde; LJ Blok. Alterations in Wnt-β-catenin and Pten signalling play distinct roles in endometrial cancer initiation and progression. J Pathol 230, 48-58 (2013)
DOI: 10.1002/path.4160

174. P Zhou; L Ma; J Zhou; M Jiang; E Rao; Y Zhao; F Guo. miR-17-92 plays an oncogenic role and conveys chemo-resistance to cisplatin in human prostate cancer cells. Int J Oncol 48, 1737-48 (2016)
DOI: 10.3892/ijo.2016.3392

175. L Fang; H Li; L Wang; J Hu; T Jin; J Wang; BB Yang. MicroRNA-17-5p promotes chemotherapeutic drug resistance and tumour metastasis of colorectal cancer by repressing PTEN expression. Oncotarget 5, 2974-87 (2014)
DOI: 10.18632/oncotarget.1614

176. H Wang; Y Zhao; L Cao; J Zhang; Y Wang; M Xu. Metastasis suppressor protein 1 regulated by PTEN suppresses invasion, migration, and EMT of gastric carcinoma by inactivating PI3K/AKT signaling. J Cell Biochem 120, 3447-3454 (2019)
DOI: 10.1002/jcb.27618

177. N Yamada; S Noguchi; T Mori; T Naoe; K Maruo; Y Akao. Tumor-suppressive microRNA-145 targets catenin δ-1 to regulate Wnt/β-catenin signaling in human colon cancer cells. Cancer Lett 335, 332-42 (2013)
DOI: 10.1016/j.canlet.2013.02.060

178. L Yang; G Xie; Q Fan; J Xie. Activation of the hedgehog-signaling pathway in human cancer and the clinical implications. Oncogene 29, 469-81 (2010)
DOI: 10.1038/onc.2009.392

179. F Wang; L Ma; Z Zhang; X Liu; H Gao; Y Zhuang; P Yang; M Kornmann; X Tian; Y Yang. Hedgehog Signaling Regulates Epithelial-Mesenchymal Transition in Pancreatic Cancer Stem-Like Cells. J Cancer 7, 408-17 (2016)
DOI: 10.7150/jca.13305

180. W Chen; T Tang; J Eastham-Anderson; D Dunlap; B Alicke; M Nannini; S Gould; R Yauch; Z Modrusan; KJ DuPree; WC Darbonne; G Plowman; FJ de Sauvage; CA Callahan. Canonical hedgehog signaling augments tumor angiogenesis by induction of VEGF-A in stromal perivascular cells. Proc Natl Acad Sci U S A 108, 9589-94 (2011)

DOI: 10.1073/pnas.1017945108

181. D Kuleszo; M Koczkowska; BS Lipska-Ziętkiewicz; W Grajkowska; E Adamkiewicz-Drożyńska; B Dembowska-Bagińska; M Ciołkowski; E Iżycka-Świeszewska. Comparative genomic analysis of intracranial germ cell tumors - the preliminary study focused on Sonic Hedgehog signaling pathway. Contemp Oncol (Poznan, Poland) 21, 279-284 (2017)
DOI: 10.5114/wo.2017.72390

182. J-S Chen; X Huang; Q Wang; J-Q Huang; L Zhang; X-L Chen; J Lei; Z-X Cheng. Sonic hedgehog signaling pathway induces cell migration and invasion through focal adhesion kinase/AKT signaling-mediated activation of matrix metalloproteinase (MMP)-2 and MMP-9 in liver cancer. Carcinogenesis 34, 10-9 (2013)
DOI: 10.1093/carcin/bgs274

183. V Fendrich; J Waldmann; F Esni; A Ramaswamy; M Mullendore; M Buchholz; A Maitra; G Feldmann. Snail and Sonic Hedgehog activation in neuroendocrine tumors of the ileum. Endocr Relat Cancer 14, 865-74 (2007)
DOI: 10.1677/ERC-07-0108

184. BL Murphy; S Obad; L Bihannic; O Ayrault; F Zindy; S Kauppinen; MF Roussel. Silencing of the miR-17~92 cluster family inhibits medulloblastoma progression. Cancer Res 73, 7068-78 (2013)
DOI: 10.1158/0008-5472.CAN-13-0927

185. F Zindy; D Kawauchi; Y Lee; O Ayrault; L Ben Merzoug; PJ McKinnon; A Ventura; MF Roussel. Role of the miR-17~92 cluster family in cerebellar and medulloblastoma development. Biol Open 3, 597-605 (2014)
DOI: 10.1242/bio.20146734

186. C Gastaldi; T Bertero; N Xu; I Bourget-Ponzio; K Lebrigand; S Fourre; A Popa; N Cardot-Leccia; G Meneguzzi; E Sonkoly; A Pivarcsi; B Mari; P Barbry; G Ponzio; R Rezzonico. miR-193b/365a cluster controls progression of epidermal squamous cell carcinoma. Carcinogenesis 35, 1110-20 (2014)
DOI: 10.1093/carcin/bgt490

187. Y Katoh; M Katoh. Hedgehog target genes: mechanisms of carcinogenesis induced by aberrant hedgehog signaling activation. Curr Mol Med 9, 873-86 (2009)
DOI: 10.2174/156652409789105570

188. L Yang; X Zhang; Y Ma; X Zhao; B Li; H Wang. Ascites promotes cell migration through the repression of miR-125b in ovarian cancer. Oncotarget 8, 51008-51015 (2017)
DOI: 10.18632/oncotarget.16846

189. BJ Henson; S Bhattacharjee; DM O'Dee; E Feingold; SM Gollin. Decreased expression of miR-125b and miR-100 in oral cancer cells contributes to malignancy. Genes Chromosomes Cancer 48, 569-82 (2009)
DOI: 10.1002/gcc.20666

190. K-Y Lin; H Ye; B-W Han; W-T Wang; P-P Wei; B He; X-J Li; Y-Q Chen. Genome-wide screen identified let-7c/miR-99a/miR-125b regulating tumor progression and stem-like properties in cholangiocarcinoma. Oncogene 35, 3376-86 (2016)
DOI: 10.1038/onc.2015.396

191. WT Budd; SJ Seashols-Williams; GC

Clark; D Weaver; V Calvert; E Petricoin; EA Dragoescu; K O'Hanlon; ZE Zehner. Dual Action of miR-125b As a Tumor Suppressor and OncomiR-22 Promotes Prostate Cancer Tumorigenesis. PLoS One 10, e0142373 (2015)
DOI: 10.1371/journal.pone.0142373

192. E Ferretti; E De Smaele; E Miele; P Laneve; A Po; M Pelloni; A Paganelli; L Di Marcotullio; E Caffarelli; I Screpanti; I Bozzoni; A Gulino. Concerted microRNA control of Hedgehog signalling in cerebellar neuronal progenitor and tumour cells. EMBO J 27, 2616-27 (2008)
DOI: 10.1038/emboj.2008.172

193. T Shibue; RA Weinberg. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. Nat Rev Clin Oncol 14, 611-629 (2017)
DOI: 10.1038/nrclinonc.2017.44

194. A Puisieux; T Brabletz; J Caramel. Oncogenic roles of EMT-inducing transcription factors. Nat Cell Biol 16, 488-94 (2014)
DOI: 10.1038/ncb2976

195. HD Tran; K Luitel; M Kim; K Zhang; GD Longmore; DD Tran. Transient SNAIL1 expression is necessary for metastatic competence in breast cancer. Cancer Res 74, 6330-40 (2014)
DOI: 10.1158/0008-5472.CAN-14-0923

196. I Pastushenko; C Blanpain. EMT Transition States during Tumor Progression and Metastasis. Trends Cell Biol 29, 212-226 (2019)
DOI: 10.1016/j.tcb.2018.12.001

197. SP Kabekkodu; V Shukla; VK Varghese; J D' Souza; S Chakrabarty; K Satyamoorthy. Clustered miRNAs and their role in biological functions and diseases. Biol Rev Camb Philos Soc 93, 1955-1986 (2018)
DOI: 10.1111/brv.12428

Abbreviations: EMT, epithelial to mesenchymal transition; miRNA, microRNA; ZEB1, Zinc finger E-box binding homeobox 1; Wnt, -wingless; ECM , extra cellular matrix; Hh, Hedgehog; FOXO1, forkhead box protein O1; PTEN, phosphatase and tensin homolog; ECM, extra cellular matrix; CDH1, Cadherin 1; CTNBB1, Catenin Beta 1; RAC1, Rac family small GTPase1; RHO, Rhodopsin; CDC42, Cell division cycle 42; PAR, partition-defective; PATJ, Protein associated to tight junctions; MMP, matrix metalloproteinases; EMT-TFs, EMT-transcription factors ; TGF-β, transforming growth factor beta; RTKs, receptor tyrosine kinases; HIF1α, hypoxia-inducible factor 1α; JAK/STAT, Janus kinase2/signal transducer and activator of transcription; TNFα, tumor necrosis factor alpha; TNFR, TNF receptor superfamily member 1A; NFkB, nuclear factor kappa B subunit 11; IKB, IKappaB; IL6, interleukin 6; EGF , Epidermal growth factor; PI3K-AKT-mTOR, Phosphoinositide-3-Kinase- AKT Serine/Threonine Kinase 1-Mammalian Target Of Rapamycin; Ras-MAPK, Rat sarcoma-mitogen-activated protein kinase 1; MKK, mitogen-activated protein kinase kinase1; *LOX*, Lysyl oxidase; HIPK1, Homeodomain Interacting Protein Kinase 1; PTEN, phosphatase and tensin homolog; SOCS1,suppressor of Cytokine Signaling 1; *CDKN1B,* Cyclin-Dependent Kinase Inhibitor 1B; GHR, Growth Hormone Receptor; TRAF3, TNF Receptor Associated Factor 3; ASCL2, Achaete-Scute Family BHLH Transcription Factor 2; FOXF2, Forkhead Box F2; CCND1, cyclinD1; SSH1, Slingshot Protein Phosphatase 1; LIMK1, LIM Domain Kinase 1; *FGFD4,* fibroblast growth factor 4; SNAIL2,

Snail Family Transcriptional Repressor 2; VIM, vimentin VIM; MDCK, madin-darby canine kidney; BRMS1L, breast cancer metastasis suppressor 1-like; ITGB1, integrin beta 1; KLF4, Kruppel-like factor 4; SNAIL1, Snail Family Transcriptional Repressor 1; MET, MET proto-oncogene; β-TRCP2, F-box and WD repeat domain containing 11; MTSS1, metastasis suppressor 1; TGIF2, TGFB induced factor homeobox; YWHAG, Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Gamma; TIMP3, TIMP metallopaptidase inhibitor 3; bHLH, basic helix-loop-helix; C19MC, chromosme19 miRNA cluster; SIP1, smad interacting protein 1; RREB1, Ras-responsive element-binding protein; PSAP, Prosaposin; GSK3β, glycogen synthase kinase 3 beta; MAGI2, membrane-associated guanylate kinase; CML, chronic myelogenous leukemia; ERK, extracellular-signal-regulated kinase; VEGF, vascular endothelial growth factor; IGF1R, insulin like growth factor 1 receptor; RAF, RAf-like-kinases; GBM, Glioblastoma; CYLD, CYLD lysine 63 deubiquitinase; RAL, RAL GTPase; RAC, RAC family small GTPase; PAK, P21 activated kinases; MLCP, myosin light chain phosphatase; MLC, Megalencephalic Leukoencephalopathy With Subcortical Cysts 1; HRAS, HRas proto-oncogene; NSCLC, non-small-cell lung carcinoma, GRB2, growth factor receptor bound protein 2; SOS, son of sevenless homolog; TRPS1, Transcriptional Repressor GATA Binding 1; HES1, Hes family transcription factor 1; BRAF, B-Raf proto-oncogene; DLK1, delta like non-canonical notch ligand; DIO3, iodothyronine deiodinase; POGLUT1, protein O-glucosyltransferase 1; LEF1, lymphoid enhancer binding factor 1; MTSS1, Metastasis suppressor protein 1; PTCH, Patched1; GLI, glioma-associated oncogene; JAG2, Jagged 2

Key Words: MicroRNA cluster, EMT, Signaling pathway, Cancer, EMT-TFs

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