Tumor suppressor microRNAs in lung cancer: An insight to signaling pathways and drug resistance

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Abstract:

Lung cancer (LC) is the second common cancer for both women and men in all over the world. Unfortunately, the number of LC deaths is increasing rapidly each year so early diagnosis of LC can be lifesaving. MicroRNAs are involved in multiple processes such as cell differentiation, transcription, inflammation, proliferation, cell signaling, and apoptosis. In LC, microRNAs function as tumor suppressors (TS) or oncogenes depending on the targets. Changes in microRNAs expression level are related to tumor initiation, progression, and metastasis. MicroRNAs can regulate gene expression and thus affect the activity status of different signaling pathways including AKT, JAK-STAT, MAPK, TGF-β, WNT, and ERK signaling pathways. Positive or negative effects on drug resistance (DR) of LC are directly affected by microRNAs and their target genes. MicroRNAs can be beneficial in combination therapy with other drugs and chemotherapeutic agents for LC.

Graphical Abstract

In this study, we will review in detail the involvement of diverse tumor suppressor microRNAs and function of their targets in different types of LC and will define their mechanism of action in different signaling pathways and review the functions of microRNAs in the development of LC drug resistance.

Keywords: Tumor suppressor, microRNA, lung cancer, drug resistance, signaling pathways

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**Introduction:**

LC is one of the main reasons for cancer-associated death in humans. Most cases of LC are identified at an advanced stage when cancer has previously metastasized and the chance for appropriate treatment is reduced [Barger and Nana-Sinkam, 2015]. There are two main types of LCs: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). About 15% of LC is SCLC, and about 85% is NSCLC. NSCLC contains lung adenocarcinoma (LUAD), large cell carcinoma (LCC) and lung squamous carcinoma (LUSC) subtypes [Inamura, 2017]. Also, in both main types of LC, carcinoid tumors can occur in the lungs that account for 1% to 2% of human lung tumors [Gilad et al., 2012; Sui et al., 2019; Wang et al., 2019]. In spite of significant advances in the treatment of LC, survival rates remain at five years because of the development of resistance to treatments [MacDonagh et al., 2015]. The leading risk factor for LC is smoking and urban air pollution; nevertheless, only a small fraction of smokers develop LC which implies that other important factors may play a key role in developing LC such as individual genetic variations and chemical agents [Danaei et al., 2005].

To date, despite the study of LC genetics and advancements in treatment and diagnosis, LC death rate has increased. The main reason for the poor prognosis and the low survival rate is the advanced stage with metastasis in most cases of LC at the time of presentation. There are different kinds of techniques for detection of LC. Some of these techniques are Narrow Band Imaging, Optical Coherence Tomography, Surgical Biopsy and Bronchial Genomic Classifier. Biopsy and Bronchial Genomic Classifier is a novel diagnosis technique with the gene expression analysis [Inage et al., 2018]. Furthermore, Epigenetic biomarkers are one of the innovative and useful methods for early diagnosis and detection of various cancers that has been confirmed in the previous research [Nikolaidis et al., 2012]. Many studies revealed the importance of regulatory mechanisms at the post-transcriptional or translational level, for example, gene regulation by non-coding RNAs such as microRNAs. These mechanisms include regulation of different genes that mediate processes like cell cycle, inflammation, apoptosis, stress responses, invasion, and differentiation [Castro et al., 2017].
MicroRNAs are a class of extremely conserved, small (19-25 nucleotides in length) single strand non-coding RNA molecules that can negatively regulate different gene expression at the post-transcriptional or translational level based on their function in RNA silencing by base-pairing with complementary mRNA molecules and leads them to the inhibition of translation through mRNA degradation. Three processes can silence mRNA molecules: (1) degradation of the mRNA, (2) Reducing mRNAs sustainability by shortening its poly (A) tail, and (3) reducing the translation efficiency of mRNA. MicroRNAs involve in different cellular processes such as transcription, cell growth, proliferation, inflammation, cell mobility, differentiation, apoptosis and cell cycle [Zhu et al., 2017]. They are usually encoded by the 3'-untranslated region (3'-UTR) or introns of genes which transcribed to a primary microRNA (pri-microRNA). Drosha, which encodes a ribonuclease (RNase) III double-stranded RNA-specific ribonuclease processes the pri-miRNA within the nucleus to a precursor microRNA (pre-microRNA). After nuclear processing, pre-microRNAs are transported to the cytosol by EXP-5. Next pre-microRNAs are cleaved and activated by the Dicer complex which is a multi-domain ribonuclease (RNase III-type) and loaded onto the Argonaute (AGO) protein which is highly conserved protein between species, to generate the RNA-induced silencing complex (RISC) (Figure 1) [Hutvagner and Zamore, 2002].

One microRNA has the ability to regulate multiple genes. On the other hand, a single gene can be regulated by different microRNAs. Thus, a single microRNA can regulate the expression level of several proteins [Macfarlane and Murphy, 2010]. MicroRNA plays a main regulatory role in gene expression and different biological processes which makes them one of the most relevant determining factors of cancer biology [Asadzadeh et al., 2019; Macfarlane and Murphy, 2010; Skrzypski et al., 2011]. MicroRNAs act as tumor suppressor genes (TSG) or oncogenes so the altered expression of them is related to several human cancers and tumors [Mardani et al., 2019; Redova et al., 2013].

Start and progression of diseases or malignancies such as LC are frequently related to aberrant regulation of microRNA expression. Various microRNAs play key roles in LC pathogenesis and have the potential to be therapeutically targeted molecules and diagnostic markers. Therefore, investigation of the role of microRNA molecules may
lead to an improved understanding of lung carcinogenesis and shed light on the therapeutic strategies and effective diagnostic to manage LC [Bagheri et al., 2019; Inamura, 2017].

Genetic alternations in TSGs and oncogenes are related to different cancers. Current data demonstrates that microRNAs also contribute to tumor development and formation indicating that microRNAs can act as TS or oncogenes (oncomir). Furthermore, tumor-associated microRNAs can serve as proper biomarkers for tumor prognosis and diagnosis [Wang et al., 2010].

Proto-oncogene is a normal gene with the normal and necessary function that could turn into an oncogene because of increased expression or various mutations. Proto-oncogenes code some proteins which regulate differentiation and cell growth. An oncogene is a mutated gene that has a high potential to cause different cancers. Oncogenes are expressed at high levels or often mutated in cancer cells. Oncogenes are the main factors of tumor growth and directly regulate metabolic signaling pathways [Nagarajan et al., 2016]. Overexpression or amplification of microRNAs may downregulate TSGs or other genes which involved in cell differentiation. MicroRNAs take part in tumor formation through stimulating invasion, proliferation, and angiogenesis acting as oncogenes in different cancers [Miska, 2005].

TSG or anti-oncogene is a protective gene that usually limits the growth of cancer cells. At the cellular level, TSGs are recessive. Therefore, inactivation of both alleles is necessary for cancer development. This is often done through mutation in first allele and deletion in the second allele. In some cases, the second allele is targeted by mutation, deletion or methylation and is led to the loss of expression. Some mutations deactivate both alleles in one event. These mutations are called dominant negative mutations. Loss of function (LOF) of TSGs inclines a cell to neoplastic transformation [Macleod, 2000]. MicroRNAs can act as TS or oncogenes depending on whether microRNAs target TSG or oncogenes (Figure 2).

TS microRNAs are frequently under-expressed in tumors and cancer cells. For example, microRNA -15, microRNA -16 and, let-7 are deleted or downregulated in leukemia and
LC, but oncomirs, such as microRNA-155 and microRNA-21, are overexpressed in tumors [Zhu et al., 2008]. In a different type of cancer, overexpressed microRNAs might act as oncogenes which promote cancer cell development through negatively regulating TSGs and other genes that control cell proliferation and apoptosis. On the other hand, underexpressed microRNAs in different cancers function as TSGs and might prevent cancer by regulating oncogenes and other genes which control different cellular process [Kazanets et al., 2016; Zhang et al., 2007]. The findings of research indicated that microRNAs act as oncomirs through targeting TSG or act as tumor suppressive microRNA through targeting oncogene. Some TSGs or oncogenes may activate microRNAs transcription through binding to promoter regions of microRNAs target genes. Epigenetic changes (mainly methylation) and mutations in microRNAs target genes, regulate microRNA expression by TSGs and oncogenes [Zhou et al., 2017b]. Abnormal expression of microRNAs regulates oncogenic genes or TSGs expression which leads to accurate detection of cancer [Lopez-Serra and Esteller, 2012].

In this study, we will review the involvement of diverse TS microRNAs and function of their targets in different types of LC in detail. Moreover, we will define their mechanism of action in different signaling pathways and review the functions of these microRNAs in the development of LC drug resistance.

**Tumor Suppressor microRNAs:**

**MicroRNA-7:**

MicroRNA-7 (miR-7) is an important microRNA that extremely conserved among various species. In human species, miR-7 expression stems from three different genomic loci: mir-7-1, mir-7-2 and mir-7-3. Mir-7-1 is located in the intron of HNRNPK gene on 9q21, hsa-mir-7-2 is in the intergenic region of 15q26 and mir-7-3 is in the intron of PGSF1a gene on 19p13. MiR-7 is involved in several human diseases and the normal development of cells [Horsham et al., 2015].

MiR-7 involved in different cellular process such as cell growth, invasion and migration of several tumors such as LC and breast cancer [Li et al., 2014].
PSME3 is one of the direct target gene of miR-7 that is located in 17q21.31. PSME3 is also called PA28gamma which is a subunit of the 11S REG-gamma and regulator of the 20S proteasome. In addition, PSME3 involve in cell growth and proliferation. MicroRNA-7 acts as a TS microRNA by negative regulation of PSME3 expression in SCLC. PSME3 is significantly upregulated and miR-7 is downregulated in NSCLC cells particularly in LUSC and LUAD. Downregulation of miR-7 might be associated with the tumorigenicity of NSCLC. Overexpression of miR-7 and silencing of PSME3 simultaneously downregulated expression level of cyclin D1 (CCND1) that leads to inhibition of NSCLC cells growth and proliferation. CCND1 gene, as a regulatory factor of the cyclin D1-CDK4 (DC) complex, encodes the cyclin-D1 protein [Chen et al., 2018; Xiong et al., 2014].

In a recent research, Xiong S et al. studied the overexpression of BCL-2 in NSCLC cells. Expression of BCL-2 at transcriptional and translational levels in NSCLC is downregulated by miR-7 through direct interactions with 3'-UTR of BCL-2 gene (Figure 3). The BCL-2 family of proteins are essential factors for the regulation of the apoptosis and mainly is found in mitochondria which is the chief controller of extracellular and intracellular signals. The members of this family are divided into two main groups including one with anti-apoptotic roles such as Bcl-XL and BCL-2 and the other with pro-apoptotic roles like BCL2 Associated X Apoptosis Regulator (Bax) and Bid. Therefore, miR-7 downregulates BCL-2 and it might be involved in the pro-apoptotic function of miR-7 in NSCLC cells [Xiong et al., 2011].

MiR-7 directly targets Paired box 6 (Pax6) in the NSCLC (Figure 4). Pax6 is a conserved transcription factor (TF) which involve in embryogenesis and development of endocrine glands. Pax6 and miR-7 mediate activities of ERK/MAPK signaling pathway. In NSCLC cells, Pax6 is significantly upregulated, while miR-7 expression is downregulated so overexpression of miR-7 can reduce the expression level of Pax6 which leads to inhibition of NSCLC cells development.

MiR-7 directly targets protein tyrosine kinase 2 (PTK2) that encodes Focal adhesion kinase protein (FAK) through ERK/MAPK signaling pathway in NSCLC cells (A549,
FAK is a Non-receptor tyrosine kinase which involves regulation of cell migration, apoptosis and proliferation. Additionally, the expression of FAK proteins is inhibited by miR-7. However, expression of FAK proteins is positively related to the expressions of MAPK and ERK, representing that ERK/MAPK signaling pathway inhibited by miR-7 through directly targeting PTK2 in NCSLC cell [Cao et al., 2016].

**MicroRNA-15a & MicroRNA-16:**

MiR-15a and miR-16, which both are located on 13q14, involve in cell cycle control and apoptosis. MiR-15a/16 are frequently downregulated in LUSC and LUAD cells. Expression level of miR-15a/16 negatively associates with the expression level of CCND1 in LUSC and LUAD tumors. The normal expression level of miR-15a/16 directly regulates CCND1, cyclin D2 (CCND2), and cyclins E1 (CCNE1) in NSCLC cell lines. Interestingly, cell cycle arrest in G1-G0 is induced by overexpression of miR-15a/16 in NSCLC [Bandi et al., 2009].

In NSCLC, miR-15a is significantly downregulated. MiR-15a directly targets BCL2L2 which is an anti-apoptotic (pro-survival) member of the Bcl-2 family of proteins and acts as an important oncogene in NSCLC. The expression level of BCL2L2 is increased in different kinds of malignancies including gastric cancer and LC. High expression level of BCL2L2 in different cancer cells increased their invasion and migration by activating the PI3K/Akt signaling pathway. Tumor stage, poor prognosis and differentiation status of LC are associated with overexpression of BCL2L2. By targeting BCL2L2, high expression level of miR-15a can reduce the cell growth via repression of apoptosis and inhibit cell migration in NSCLC cells (Figure 3) [Xu et al., 2012; Yang et al., 2015c].

MiR-15a/16 and miR-34 contain very distinct seed sequences but they are associated functionally. MiR-15a/16 and miR-34 share the same targets including CCND1, Bel-2 and E2F3. However, miR-15a/16 have other targets that are unique, such as CCNE1, CCND2, and cyclin D3 (CCND3). In a complex, Cyclin D with Cyclin-dependent kinase 2 (CDK2) regulate progression of the cell cycle through the boundary of G1 phase to S.
phase. These complexes phosphorylate Retinoblastoma (Rb) protein and phosphorylation of Rb protein inhibit it from binding to E2F which is an important transcription factor and drives cells from G1 phase to S phase. Finally, the cell cycle arrested in G1-G0 is induced by miR-15a/16 in NSCLC cells [Bandi and Vassella, 2011].

Li Minjie et al. shows that low expression level of miR-15a enhances cell invasion and proliferation of NSCLC cells. Furthermore, downregulation of this microRNA in NSCLC cells, decreased the expression of E-cadherin, although increased those of vimentin and N-cadherin. Cadherins are important in the formation of adherens junctions. Furthermore, E-cadherin is an Epithelial Mesenchymal Transition associated (EMT) protein. EMT is a biologically highly dynamic process that epithelial cells miss their polarity and cell to cell adhesion, and gain immigration feature and invasive properties to become mesenchymal stem cells. It occurs during normal embryonic development, wound healing, organ fibrosis, and tissue regeneration. A main feature of EMT is the upregulated expression level of vimentin and N-cadherin and the low expression level of E-cadherin. Low expression level of miR-15a leads to increase the expression of vimentin and N-cadherin and able to downregulate the expression level of E-cadherin. These proofs suggest that the expression level of E-cadherin in NSCLC cells may be related to the downregulated miR-15a on the EMT. In conclusion low expression level of miR-15a in NSCLC cells promotes EMT and its overexpression inhibits EMT [Alidadiani et al., 2018; Li et al., 2017; Tulchinsky et al., 2019].

MiR-16 is important in regulating cell differentiation and self-renewal. MiR-16 downregulated in NSCLC, LUAD and, LUSC cells. MiR-16 directly targets Autophagy related 3 (ATG3) which is involved in autophagy of NSCLC cells (Figure 3). In patients with NSCLC, ATG3 is significantly upregulated and miR-16 is significantly downregulated. ATG3 and miR-16 are involved in TGF-β1-modulated NSCLC cell function. TGF-β1 is essential for the induction of EMT and regulating autophagy-induced EMT. In conclusion, TGF-β1-induced EMT is inhibited by miR-16 in NSCLC cells by activation of autophagy through regulating ATG3 [Soleimani et al., 2019; Wang et al., 2018].
MicroRNA-26:

The microRNA-26 family includes three members of miR-26a-1, a-2 and b. MiR-26a-1/2 have an identical sequence which differs from the miR-26b. Zhu Y et al. indicated that that miR-26 family blocks G1 to S phase transition in LC [Zhu et al., 2012]. Solomides CC et al. demonstrated that miR-26 is downregulated in different cancers such as hepatocellular carcinoma and NSCLC [Solomides et al., 2012].

MiR-26 family can directly target different genes and regulate important pathway. For instance, miR-26b can directly target Mcl-1 in SCLC cells (Figure 3 and 5). Mcl-1 is an important anti-apoptotic member of the Bcl-2 family of protein. Mcl-1 is expressed at a high level in human cancers and suppressed by miR-26b [De Blasio et al., 2018; Yu et al., 2018a].

MiR-26b directly targets and regulates Migration and invasion enhancer 1 (MIEN1) expression in NSCLC cells. MIEN1 is also called ORB3 or C35, located in the chromosome 17, encodes MIEN1 protein which is of primary importance in the regulation of apoptosis, through controlling of caspase-3 (CASP3) and its overexpression increases cell migration. In NSCLC cells, miR-26b targeted MIEN1 through NF-κB/MMP-9/VEGF signaling pathway and inhibited cell migration and invasion. NF-κB is a transcription factor that controls cell survival and production of cytokine. Matrix metalloproteinase 9 (MMP-9) which is a downstream target gene of NF-κB pathway, is involved in migration of NSCLC cells. MIEN1 changes MMP-9 expression levels by regulating the NF-κB pathway. In conclusion, the expression level of MMP-9 and NF-κB are increased by overexpression of MIEN1[Li et al., 2016a; Noruzi et al., 2018; Zhou et al., 2017a].

MiR-26a regulates Lin-28 homolog B (LIN28B) via direct binding of its 3'-UTR in NSCLC cells. LIN28B is a suppressor of microRNA biogenesis also known as an oncogenic driver that is intensely upregulated in NSCLC compared to normal cells. Overexpression of miR-26a reduces LIN28B expression. Inhibited LIN28B leads to an upregulation of STAT3 and Interleukin 6 (IL6) and balances the enhancement of invasion and metastasis in NSCLC cells. Remarkably, the expression of STAT3 and IL6 are

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decreased by silencing \( \text{LIN28B} \) in NSCLC cells. In conclusion, \( \text{LIN28B} \) is one of the main target gene of \( \text{miR-26a} \) and main downstream mediators of \( \text{LIN28B} \) are \( \text{STAT3} \) and \( \text{IL6} \) in the LC cell metastatic processes [Lu et al., 2018; Siveen et al., 2014].

\( \text{MiR-26a/b} \) inhibits migration, invasion, and proliferation of LC cells by targeting cell division cycle 6 (\( \text{CDC6} \)) in LC cells directly. \( \text{CDC6} \) is an important factor for loading the helicase minichromosome maintenance protein complex (MCM) proteins onto replication origins. \( \text{CDC6} \) encodes Cell division control protein 6 homolog that participates in checkpoint controls. Regulation of replication-initiation proteins is not only critical for preventing cancer but also vital for certifying genetic inheritance in normal cell cycle progression. \( \text{MiR-26a} \) and \( \text{miR-26b} \) certainly suppress \( \text{CDC6} \) gene expression by binding to 3'-UTR of the \( \text{CDC6} \) gene that inhibits LC cells development through preventing the loading the helicase MCM proteins onto replication origins [Zhang et al., 2014].

**MicroRNA-29:**

The microRNA-29 (\( \text{miR-29} \)) family includes 3 members of \( \text{miR-29a, b, and c} \). Abnormal expression of all \( \text{miR-29} \) family members, which have anticancer roles, has been observed in various cancer cells [Yan et al., 2015; Zierau et al., 2018].

\( \text{MiR-29} \) family can target Lysyl oxidase-like 2 (\( \text{LOXL2} \)) in LUSC directly (Figure 4). \( \text{LOXL2} \) is a well-known oncogene and an enzyme that changes the structure of histones and therefore changes the shape of the cells which leads to metastasize of cancer cells. Furthermore, overexpressed \( \text{LOXL2} \) is confirmed in LUSC cells and silencing of \( \text{LOXL2} \) inhibited invasion and migration of LUSC cells [Mizuno et al., 2016].

Wnt signaling pathway is suppressed by \( \text{MiR-29} \) family through demethylation of Wnt inhibitory factor-1 (\( \text{WIF-1} \)) in NSCLC (Figure 6). DNA methyl-transferases (\( \text{DNMTs} \)) are a group of enzymes cause the abnormal DNA methylation of TSGs which methylate CpG residues. Min Tan et al have reported overexpression of \( \text{DNMT3A, DNMT3B, and DNMT1} \) in different types of cancers. \( \text{DNMTs} \) overexpression is correlated with hypermethylation of TSGs [Tan et al., 2013].

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MiR-29c downregulates MMP2 and integrin beta-1 (ITGB1) directly by targeting the 3'-UTR sequence which reduces the protein levels of ITGB1 and MMP2. MMP2 gene encodes a protein called 72-kDa type IV collagenase which involve in migration, proliferation, invasion, and adhesion. MiR-29 can reduce MMP2 enzyme activity by binding to its 3'-UTR site which leads to suppression of LC cell adhesion to extracellular matrix (Figure 3) [Wang et al., 2013b].

MiR-29c acts as a TS by targeting vascular endothelial growth factor A (VEGFA) in LUAD (Figure 6). VEGFA is involved in endothelial cell growth and angiogenesis. Overexpression of VEGFA promotes cell migration and inhibits apoptosis. Recent studies indicated that VEGFA is overexpressed in many cancers including LC and contributes to poor prognosis. MiR-29c targets VEGFA as a downstream gene and acts as a TS microRNA in LUAD [Liu et al., 2017].

AKT Serine/Threonine Kinase 2 (AKT2) is an important oncogene which is targeted and is negatively regulated by miR-29c (Figure 4 and 6). Overexpression of AKT2 has been reported in different cancers such as LC. Therefore, miR-29c acts as a TS microRNA in LC. AKT2 is serine/threonine-protein kinases also is called the RAC-beta serine/threonine-protein kinase or AKT kinase. AKT2 regulates different cellular processes including proliferation and angiogenesis [Sun et al., 2018].

MicroRNA-134:

MiR-134 is found on chromosome 14q32 and is dysregulated in various cancers, for instance, glioma, breast, colorectal and LC. MiR-134 is a well-established TS microRNA. Abnormal expression of miR-134 has been reported in various human cancers such as ovarian and LC. MiR-134 also involve in tumor cell invasion, metastasis, drug resistance, proliferation and apoptosis [Pan et al., 2017]. The aberrant expression of miR-134 is related to EMT phenotype and invasion of NSCLC cells. Li J et al. indicates that EMT is inhibited by miR-134 in NSCLC cells. Furthermore, Forkhead box protein M1 (FOXM1) is a functional and direct target of miR-134 (Figure 6). FOXM1 is an oncogenic gene and a potential metastasis promoter. Most significant molecular markers of EMT are gain of Vimentin and loss of E-cadherin expression. Many studies indicate that microRNAs act

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as essential modulators for EMT. Moreover, Knockdown of FOXM1 through miR-134 reverses EMT in NSCLC cells. FOXM1 is one of the important members of forkhead box transcription factors family which takes part in TGFb1-induced EMT in NSCLC cells. Overexpression of FOXM1 is related to invasion and early steps of metastasis of human LC [Huang et al., 2014; Li et al., 2012].

MiR-134 can inhibit NSCLC colony formation, proliferation, invasion, migration, and stimulated cell apoptosis through targeting 3’-UTR of the cyclin D1 gene (CCND1) (Figure 5 and 6). CCND1 gene encodes Cyclin D1 protein which is an oncogene that revealed a lot of oncogenicity power through the increase of migration, invasion, and EMT [Sun et al., 2016]. ITGB1 is a direct and functional target of miR-134 in NSCLC cells. ITGB1 is a cell surface receptor and is involved in angiogenesis and promoting endothelial cell motility. MiR-134 downregulates ITGB1 expression and inhibits EMT in NSCLC cells [Qin et al., 2017].

MiR-134 targets the epidermal growth factor receptor (EGFR) directly in NSCLC cells (Figure 3). The EGFR belongs to the ERBB family which activates different signaling pathways to convert extracellular signals into proper cellular responses. EGFR is often abnormally activated in different cancers such as NSCLC. EGFR signaling includes 3 main signal transduction pathways which are RAS/RAF/MEK/ERK, STAT3-dependent signaling, and PI3k/AKT. In NSCLC, miR-134 downregulates EGFR and suppresses specific EGFR associated signaling. MiR-134 inhibits growth and proliferation of LC cells by cell cycle arrest and induces cell apoptosis through targeting of EGFR [Qin et al., 2016].

MicroRNA-138:

MiR-138 is an extremely conserved microRNA amongst mammals [Xu et al., 2014]. Among the microRNAs, miR-138 has recently appeared as a significant TS in various cancers such as osteosarcoma, and NSCLC. MiR-138 induces apoptosis, inhibits proliferation, invasion, metastasis, and increases chemo-sensitivity of LC cells through the inhibition of several targets [Sha et al., 2017].
In NSCLC cells, *mir-138* significantly downregulated and interestingly, upregulation of *miR-138* can inhibit cell growth through targeting *EZH2* which is a functional and direct target of *mir-138*. *EZH2* is responsible for the methylation activity of a complex which includes EED, SUZ12, and PCL. These are the group proteins that are required for optimal function of *EZH2*. Additionally, the expression level of *EZH2* is reduced by overexpression of *mir-138* in NSCLC. The binding site of *mir-138* is recognized in the 3'-UTR of *EZH2* mRNA (Figure 4) [Sanna et al., 2018; Zhang et al., 2013b].

*MiR-138* is identified as potential TS that regulates *PDK1* expression in NSCLC cells (Figure 4). *PDK1* is involved in different processes including differentiation, apoptosis, and cell proliferation. Furthermore, *miR-138* can inhibit proliferation of NSCLC cells by targeting *PDK1* which suggests the key role of *miR-138/PDK1* cascade in NSCLC [Han et al., 2014].

Upregulation of *miR-138* inhibits cell division and growth in NSCLC. Cyclin D3 (*CCND3*) is one of the target genes of *miR-138*. Cyclin D3 is a member of the cyclin D family which involve in the G to S transition in the cell cycle. Upregulation of *miR-138* leads to repression of *CCND3* in NSCLC cell lines that suppresses G to S transition in NSCLC cells [Han et al., 2016].

*MiR-138* overexpression induced the reversion of EMT with increased E-cadherin and *ZO-1* expressions and reduced Slug (*SNAI2*) expression accompanied by reduced invasion and migration capabilities. *SNAI2* gene encodes a protein with nucleic acid binding fingers which acts as a transcriptional repressor in different cancer cells. *SEMA4C* (Semaphorin 4C) and *GIT1* are direct and functional targets of *miR-138*, both critical for the development of NSCLC Epithelial Mesenchymal Transition (Figure 4 and 6). *SEMA4C* is a protein-coding gene that encodes an important member of the Semaphorin family of proteins having various functions in immune cell regulation, tumor progression, and vascular growth. *GIT1* gene encodes ARF GTPase-activating protein GIT1 that is an enzyme involved in phosphorylation and inhibition of the Adrenoceptor Beta 2 (*ARDB2*) [Li et al., 2015].

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**MiR-138**

MiR-138 is an upstream regulator of forkhead box P4 (FOXP4) in NSCLC cells. Overexpression of miR-138 suppresses FOXP4 at the transcription level. Many members of the Forkhead box (FOX) gene family, including FOXP4, have roles in human oncogenesis. All members of the forkhead box family have a forkhead domain (FKH) that acts as a transcriptional repressor or activator. FOXP4 is independently related to the miR-138 regulatory pathway in NSCLC cells [Yang et al., 2015b].

**MicroRNA-148:**

The mir-148/152 family is composed of 3 extremely conserved microRNAs including mir-148a, b, and mir-152. Mature microRNA is generated from mir-148/152 family has similar structures, sequences, and an identical seed region. In humans, mir-148a, mir-148b, and mir-148b are located in chromosomes 7p15.2, 12q13.13 and 17q21.32, respectively [Li et al., 2016b]. The downregulated expression of mir-148a can be detected in different cancers such as colorectal cancer and NSCLC [Yang et al., 2015a].

Chen Y et al. shows that Wnt family member 1 (Wnt1) is a functional and direct target of mir-148a. Wnt signaling pathway regulates critical features of cell destiny determination, cell migration, polarity, and organogenesis during embryonic development. Mir-148a expression correlates negatively with the expression of Wnt1 in LC. Furthermore, the expression of Wnt1 protein is inhibited by overexpression of mir-148a which reduces cell invasion and migration in LC cells (Figure 6) [Chen et al., 2017b].

**ROCK1** is a potential metastasis promoter which is directly targeted by miR-148a (Figure 4). ROCK1 protein is a serine/threonine kinase and is a key member of the Rho family of GTPase proteins. ROCK1 is widely upregulated in NSCLC and is negatively correlated with miR-148a expression. MiR-148a reduces the expression of ROCK1 protein which leads to a decrease in cell invasion and migration and reversed EMT in NSCLC cells [Li et al., 2013].

**MiR-148b** involves in cancer progression and tumorigenesis. MiR-148b suppresses the invasion, migration, and proliferation of NSCLC cells through directly targeting Carcinoembryonic antigen (CEA) pro-oncogene. CEA encodes a cell surface glycoprotein

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that is a member of the carcinoembryonic antigen family of proteins. CEA protein promotes tumor development through its role as a cell adhesion molecule. Moreover, CEA protein regulates cell polarity, apoptosis, and differentiation. CEA is upregulated in NSCLC specimens and its mRNA levels are negatively associated with miR-148b expression [Liu et al., 2014].

MicroRNA-195:

MiR-195 is a member of the miR-15/16 family which includes five microRNAs (miR-15a, miR-15b, miR-16-1, miR-16-2 and, miR-195). Many studies have reported that miR-195 has diverse effects on cell growth and apoptosis in different cancers such as LC. Abnormal expression of miR-195 has been reported in various cancers such as gastric cancer and NSCLC [Flavin et al., 2009; Yongchun et al., 2014; Yu et al., 2018b].

MiR-195 acts as TS microRNA in NSCLC through directly targeting Bcl-2, CCNE-1, and MYB proto-oncogene, transcription factor (MYB), and negatively regulating their expression (Figure 3 and 5). Myb genes are members of a large gene family of transcription factors found in animals and plants. In humans, Myb genes contain two main members including Myb proto-oncogene like 1 (MYBL1) and Myb-related protein B (MYBL2). CCNE-1 is an important oncogene and involve in cell proliferation and oncogenesis. MiR-195 is downregulated in NSCLC cells but its overexpression results in reduced MYB, BCL2 and, CCNE1 expression which leads to suppression of NSCLC cells development [Yongchun et al., 2014].

MiR-195 regulates apoptosis, cellular senescence and cell cycle progression of NSCLC cells. CCND3 is directly targeted by miR-195 which cause to cell cycle’s arrestment at the G1 phase. MiR-195 also targets Survivin which is also called BIRC5 (Figure 5 and 6) [Yu et al., 2018b]. One of the direct and functional targets of miR-195 is IGF1R which is crucial for tumor transformation and survival of LC cells and plays a critical role in regulating different cellular processes, such as differentiation, survival, motility, and growth. In LC cells, IGF1R is generally overexpressed and plays a significant role in tumorigenesis [Wang et al., 2015].

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**MicroRNA-203:**

*MiR-203* is located on 14q32.33 and is involved in skin diseases. *MiR-203* is also served as a TS microRNA by regulating different biological processes including differentiation, metastasis, invasion, cell mobility and apoptosis in various cancers such as LC [Jin et al., 2013; Li et al., 2019; Zierau et al., 2018].

*MiR-203* functions as TS microRNA by directly targeting *Bmi1* in NSCLC cells. *Bmi1* is a member of a Polycomb group (PcG) multiprotein PRC1-like complex. *MiR-203* is downregulated but *Bmi1* is upregulated in NSCLC cells. Overexpression of *miR-203* suppresses *Bmi1* expression which cause to inhibition of proliferation and growth in NSCLC cells [Chen et al., 2015].

Cluster of Differentiation 82 (*CD82*) is a metastasis suppressor. *CD82* prevents the Wnt signaling pathway through downregulation of Frizzled (FZD) isoforms which is a family of GPCR proteins that act as receptors in the Wnt signaling pathway. *CD82* causes the upregulation of *miR-203* and directly downregulates Frizzled2 (*FZD2*) expression [Mine et al., 2015]. *MiR-203* directly identifies and binds to 3'-UTR of *SRC* mRNA and inhibits *SRC* translation. *SRC* protein acts as an oncogene and is involved in tumor progression through promoting the proliferation, survival, and invasion of LC cells. *SRC* protein also regulates several signaling pathways related to tumor progression and development, such as FAK signaling pathway that is also known as PTK2 which is involved in cellular spreading and adhesion processes. *SRC* expression is inhibited by *miR-203*, which activates the suppression of the SRC/Ras/ERK signaling pathway which finally suppressed the migration, invasion and induced the apoptosis of LC cells (Figure 4) [Wang et al., 2014].

*PKCα* is a direct target of *miR-203*. PKC involved in different signal transduction pathways. The PKC family encloses ten associated isoforms with different cofactor requirements. The level of *PKCα* protein is higher in NSCLC cells compared to normal cells; thus, one of the general features of NSCLC cells increased the expression of *PKCα*. *MiR-203* identifies the 3'-UTR of the *PKCα* mRNA and downregulates its expression in LC cells (Figure 6) [Wang et al., 2013a].

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RGS17 is a direct and functional target of miR-203. Interestingly, upregulation of miR-203 suppresses the growth of LC cells through inhibiting RGS-17 in transcription level. RGS-17 is located on 6q25.3 and encodes a member of the RZ family of RGS proteins which is reported to be overexpressed in different cancers such as hepatocellular carcinoma and human LUAD. RGS protein increases the rate of GTP hydrolysis. Moreover, the increased expression level of RGS17 protein has been positively associated with tumor cell proliferation through the CAMP-PKACREB pathway in human LC [Chi et al., 2017].

MicroRNA-218:

MiR-218 is located on 4p15.31 and 5q35.1 and is recognized as TS microRNA in NSCLC. MiR-218 is co-expressed simultaneously with its host genes. Slit Homolog 2 Protein (SLIT2) and Slit Homolog 3 Protein (SLIT3) are two members of the SLIT family and are the host genes of miR-218. Aberrant expression of miR-218 is reported in various cancers, such as bladder and NSCLC [Yang et al., 2017; Zhang et al., 2017].

Tumor protein D52 (TPD52) is directly regulated via miR-218. TPD52 protein is involved in plasma membrane based exocytic and endocytic function in LUAD. One of the most important amplified genomic regions is 8q21.13 which includes TPD52 gene. Overexpression of TPD52 is reported in SCLC, LUAD, and LUSC. Overexpression of TPD52 is detected in LUSC clinical specimens. Furthermore, downregulation of the TPD52 gene inhibited cancer cell invasion and metastasis. MiR-218 can inhibit invasion and migration of LC by directly targeting 3'-UTR of TPD52 gene [Kumamoto et al., 2016].

MiR-218 plays an anti-metastatic role, which is based on inhibiting cell invasion and migration in NSCLC cells through directly targeting HMGB1. Overexpression of HMGB1 is related to cancer cells migration and is involved in the development of different cancers including melanoma, colon, and LC. HMGB1 promotes the cell invasion through regulation of MMP-9 in LC. Moreover, miR-218 suppresses HMGB1 expression and reduces invasion and migration of LC cells through regulation of MMP-9 [Zhang et al., 2013a].

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EMT and EMT-related traits are inhibited by overexpression of *miR-218* through targeting the *ZEB2* and *Slug* (*Snail 2*), which is an EMT regulator, in vivo and in vitro. *Slug* and *ZEB2* are known to be related to EMT and tumor metastasis. *MiR-218* downregulates *Slug* and *ZEB2* expression level by directly targeting their 3′-UTR regions (Figure 4 and 6). Furthermore, high expression level of *miR-218* increases the chemosensitivity of H1299 cells to cisplatin by suppression of *ZEB2* and *Slug* [Shi et al., 2017].

*EGFR* is a direct target of *miR-218*. The correlation between EGFR protein levels and *miR-218-5p* is an inverse correlation in NSCLC. Expression of *EGFR* is negatively regulated by *mir-218* which leads to inhibiting EGFR translation in NSCLC (Figure 3) [Zhu et al., 2016].

*MEF2D* is a direct target of *miR-218*. MEF2 proteins involved in gene expression, stress response, cellular differentiation, and embryonic development. *MEF2D* is overexpressed in LC tissues and cell lines. Furthermore, transcription of *MEF2D* is negatively regulated by *miR-218* in LC cells. High expression level of *miR-218* suppresses the expression of *MEF2D* in LC cells, which cause to inhibition of cancer cells development [Song et al., 2016].

**MicroRNA-320:**

The *miR-320* family is a highly conserved microRNA but only found in vertebrates. This family contains five members: *miR-320-a*, *miR-320-b*, *miR-320-c*, *miR-320-d* and, *miR-320-e*. *MiR-320-d* and *miR-320-e* exist only in humans and primates. The *miR-320a* is located on 8p21.3, while the *miR-320b-1* and *miR-320b-2* are located on 1p13.1 and the *miR-320c-1* and *miR-320c-2* are located on 18q11.2. *MiR-320* is downregulated in different tumors compared with normal tissue, for instance, in prostate cancer and NSCLC [Lei et al., 2016; Li et al., 2018; Lieb et al., 2017; Zhao et al., 2018].

*MiR-320a* is an important TS microRNA that increases the sensitivity of cancer cells to chemotherapy. *MiR-320a* directly regulated *STAT3* expression in LUAD cells (Figure 3). *STAT3*, a member of the JAK/STAT3 signaling pathway, is the most important player in several pathological and physiologic processes, such as cell survival, growth and

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proliferation in different cancers as well as in immune diseases. *MiR-320a* suppresses *STAT3* signals and suppression of *STAT3* signals induce apoptosis and reduce cell proliferation [Lv et al., 2017].

*MiR-320* inhibits NSCLC cells invasion and migration through directly targeting Fas cell surface death receptor (*FAS*), which is an essential protein for cancer metastasis, invasion, and proliferation. *FAS* gene encodes a protein named TNFSF6, a multifunctional enzymatic complex. In normal human tissue the endogenous *FAS* is expressed at low levels. Nevertheless, the expression level of *FAS* is extremely upregulated in cancer cells which leads to metastasis and proliferation of different types of cancer, such as colorectal, bladder and LC. Additionally, the expression of *FAS* at the translational level reduced through *miR-320* expression in NSCLC cells. In conclusion, *miR-320* acts as TS in NSCLC cells via directly targeting *FAS* [Lei et al., 2016].

*SND1* acts as a metastasis activator and directly targeted by *miR-320a* in LC cells (Figure 5). *SND1* also known as *p100* is an endonuclease that mediates microRNA decay of both protein-free and AGO2-loaded microRNAs and acts as a transcriptional coactivator for *STAT5*. *P100* is upregulated in human LC cells and is involved in cancer cell metastasis and invasion. *P100* is directly targeted by *miR-320a* through its 3'-UTR binding site which leads to inhibition of *P100* and reduces metastasis and invasion of LC cells [Xing et al., 2018].

**MicroRNA-449a:**

*MiR-449a* is located on 5q11.2 which is an important recognized region in different cancers such as LC. *MiR-449a* is recognized as TS microRNA. *MiR-449a* is downregulated in different types of cancers including bladder cancer and endometrial cancer [Chen et al., 2012].

*MiR-449a* acts as an important metastasis suppressor in various cancers. Overexpression of *miR-449a* suppresses migration and invasion of NSCLC cells. Furthermore, *miR-449a* mediates the metastasis-suppressing activity of NSCLC cells via modulating Polycomb Repressive Complex 2 Subunit (*SUZ12*) expression. You J et al. indicated that Mitogen-
activated protein kinase 1 (MAP2K1 or MEK1) is a direct and functional target of miR-449a. Moreover, the MAPK signaling pathway is involved in NSCLC metastasis that regulated by miR-449a. Interestingly, miR-449a expression is directly regulated by Activator protein 1 (AP-1) through a negative feedback loop (Figure 4). AP-1 is an important TF which regulates gene expression level in response to different stimuli including stress, and cytokines [You et al., 2015]. MiR-449a plays a TS function through targets the E2F3 gene which results in inhibition of cell proliferation and induction of cell senescence-like phenotype in LC cells. E2F3 is a member of the E2F family that is frequently dysregulated during tumorigenesis and overexpressed in different cancers, such as LC. E2F3 is an important regulator of G1 to S transition and has major role in regulating both cell proliferation and apoptosis. E2F3 is overexpressed in almost all LC tumors and cell lines. E2F3 gene is downregulated by overexpression of miR-449a in LC cells which leads to suppression of G1/S transition of cancer cells [Ren et al., 2014].

**Drug-resistance in Lung cancer:**

The main cause for chemotherapeutic failure is drug-resistance (DR). Chemotherapy is the principal treatment for patients with LC. Multidrug resistance (MDR) is one of the main factors that makes outcome undesirable. Chemotherapy is considered as the first strategy for the treatment of LC. Wide molecular profiling studies identify the different drug-gable target for LC therapy. A variety of effective therapeutic molecules is specifically targeting signaling pathways and oncogenic mutations driving lung carcinogenesis have been successfully tested and developed in the clinical filed. Nevertheless, due to the detected DR, the effectiveness of chemotherapy is extremely limited which results in poor survival rate. Several molecular mechanisms such as changes in drug targets, mutations restoring DNA repair function, high drug efflux, deregulated apoptosis, and activation of survival signaling pathways contribute to DR. Aberrant regulation of microRNA affects the expression of genes involved in DR mechanisms including DNA damage repair, cell cycle control, and apoptosis [Ghasabie et al., 2019].

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**MicroRNA-7:**

According to Liu et al. reports, in patients with SCLC, the downregulation of miR-7 is not related to sex, age, and stage of SCLC. It correlates with the survival rate and the reaction of patients to drugs. Multidrug resistance-associated protein 1 (MRP1) is an important protein in DR of different cancers and is encoded by the *ABCC1* gene (Table 1). There is a reverse correlation between the expression of MRP1 and miR-7. Interestingly, in SCLC cells expression level of MRP1 is downregulated by overexpression of miR-7. Provide evidence endorse that miR-7 suppresses MRP1 with binding to 3’-UTR of its gene. Therefore, it mediates SCLC chemo-resistance which is a significant procedure of chemo-resistance, potential therapeutic target and prognostic predictor SCLC [Liu et al., 2015a].

**MicroRNA-16:**

Paclitaxel-based on combination chemotherapy is used widely which may prolong survival in LC patients. Chatterjee et al. reported that in paclitaxel-resistant LC cells, miR-16 is significantly downregulated. Paclitaxel stabilizes microtubule and arrests mitosis. Furthermore, paclitaxel is the cause of apoptosis in LC cells by regulation of expression of the cytokine gene and interacting with the membrane proteins of Mitochondria. Chatterjee et al. show that one of the targets of miR-16 in paclitaxel-resistant LC cells is *Bcl-2*. Therefore, Overexpression of miR-16 remarkably decreases the expression of Bcl-2. Overexpression of Bcl-2 is found in various cancers and is connected with the expansion of chemo-resistance in LC. In addition, it is discovered that if miR-16 overexpresses and paclitaxel is used for treatment enormously, the paclitaxel-resistant LC cells sensitize to paclitaxel. Therefore, they are led to apoptosis through the caspase-3 pathway. Bcl-2 overexpressed is related to the development of chemo-resistance in LC cells (Table 1). Bcl-2 expression is significantly reduced by Overexpression of miR-16 [Chatterjee et al., 2015; Fahy et al., 2005; Ferlini et al., 2009].
MicroRNA-26a/b:

Chen et al. show that $EZH2$ is a direct and functional target of $miR-26a$ (Figure 4). In docetaxel-resistant LUAD cells overexpression of $miR-26a$ downregulates $EZH2$ which reduces cell growth and proliferation and increases apoptosis. Furthermore, downregulation in $EZH2$ expression reverses EMT (Table 1). $MiR-26a/EZH2$ signaling pathway involved in the malignancy of docetaxel-resistant LUAD cells showed that $miR-26a$ involve in the molecular etiology of chemo-resistant LUAD cells [Chen et al., 2017a].

MicroRNA-29c:

Sun et.al show that oncogene $AKT2$ is a functional and direct target of $miR-29c$ and is negatively regulated by this microRNA (Figure 4 and 6). $AKT2$ encodes RAC-beta serine/threonine-protein kinase in humans which regulate several processes such as angiogenesis, proliferation and cell growth (Table 1). Furthermore, the PI3K/Akt signaling pathway is negatively regulated by $miR-29c$ which leads to cisplatin sensitivity of NSCLC cells. $MiR-29c$ overexpression significantly raises the cisplatin sensitivity of NSCLC cells. Nevertheless, cisplatin resistance of NSCLC cells is increased by knocking down of $miR-29$. $AKT2$ and $Antigen ki-67$ index expression is decreased by both $miR-29c$ overexpression and cisplatin treatment in NSCLC cells. Ki-67 is an important protein encoded by the Marker of Proliferation Ki-67 (MKI67) gene in humans. In conclusion, co-treatment of NSCLC cell with cisplatin and $miR-29c$ inhibit migration and invasion [Sun et al., 2018].

MicroRNA-148:

Su et al. compared cisplatin resistant NSCLC cell line (A549/DDP) and parental A549 cell line. The findings showed the downregulation of $miR-148b$ and contrary to its upregulation of $DNMTs$. Interestingly, overexpression of $miR-148b$ is the cause of the decline in the expression of $DNMT1$ in A549 and A549/DDP cells. Besides, they increase cisplatin sensitivity of A549/DDP cells and lead them to apoptosis. Nevertheless, an inhibitor of $miR-148b$ enhances $DNMT1$ expression (Table 1). In sum, over-expressed
DNMT1 inverts pro-apoptosis impact of miR-148b and silenced DNMT1 increases the sensitivity of A549/DDP cells to cisplatin [Sui et al., 2015].

**Conclusion:**

Different expressions for several microRNAs have been discovered in LC. These different expressions are tumor- and tissue-specific. This review can shed light on accomplishing diagnosis and treatment of LC. Therefore, establishing a signature microRNA expression profile based on detailed studies of different microRNAs and their targets can help its prognosis, early diagnosis and classification. In addition, probably the novel strategies for the treatment of LC may be offered by focusing on aberrations in the expression of microRNAs and how they may be regulated. According to above-mentioned research, distinct microRNA expression profiles in the body fluids and exhaled breath of LC patients have been identified which can act as potential exhaled breath and blood-based biomarkers for LC diagnosis.

Furthermore, the expression level of distinct microRNAs increases in body fluids and exhaled breath of patients with metastatic LC compared with patients with non-metastatic LC. As a result, they are suggested as new prognostic markers. Therefore, to diagnose LC precisely, it is possible that microRNAs combined with other diagnostic tests can be used jointly as potential biomarkers. Despite being in the early developmental stages towards these novel therapeutic strategies, based on the most recent research we believe that some microRNAs should be served as potential therapeutic tools for monotherapy or combination therapy of LC with available medical treatments and could be promising in terms of therapeutics in near future. Due to the tumor suppressive properties of
microRNAs, they are likely to be used as therapeutic targets and biomarkers for LC treatment because cancer is not defeated without a fight.

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**Conflict of interest**

All the authors declare no conflict of interest.

**Reference:**


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Figures

Figure 1. Biogenesis and function of microRNA. Biogenesis of microRNA starts with the generation of the pri-miRNA transcripts by RNA pol II/III. The microprocessor complex, comprised of DGCR8 and Drosha, cleaves the pri-miRNA to generate the pre-miRNA. Then, the pre-miRNA is exported to the cytoplasm through Exportin5/RanGTP. Next pre-microRNAs are cleaved and activated by the Dicer complex (Dicer and TRBP). Finally, strands of the mature microRNA duplex are loaded into the Argonaute to produce the RISC. Mature microRNA leads to translational repression or mRNA target cleavage.

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Figure 2. TS microRNA vs oncogenic microRNA. MicroRNAs can act as TS by targeting oncogene which leads to development of normal cells or act as oncogenic microRNA (OncomiR) by targeting TSG, leads to development of cancer cells.

Figure 3. EGFR, JAK-STAT, m-TOR, AKT and related signaling pathway and microRNA in lung cancer.
**Figure 4.** MAPK/ERK, FAK, AKT and related signaling pathway and microRNA in lung cancer.

**Figure 5.** RTK and Wnt signaling pathway and microRNA in lung cancer.

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Figure 6. Wnt, TGFB, RTK, TNFR, MAPK/ERK, AKT and related signaling pathway and microRNA in lung cancer.

Table 1. Drug resistance microRNAs in LC

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>Target</th>
<th>Protein name</th>
<th>Cancer</th>
<th>Signaling pathway</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>MicroRNA -7</td>
<td>ABCC1</td>
<td>Multidrug resistance-associated protein 1 (MRP1)</td>
<td>SCLC</td>
<td>-----------------------------</td>
<td>[Liu et al., 2015b]</td>
</tr>
<tr>
<td>MicroRNA -16</td>
<td>Bcl-2</td>
<td>Bcl-2-like protein 2</td>
<td>NSCLC</td>
<td>PI3k/AKT, IL-6/JAK/STAT3</td>
<td>[Chatterjee, 2015]</td>
</tr>
<tr>
<td>MicroRNA -26a/b</td>
<td>EZH2</td>
<td>Histone-lysine N-methyl transferase EZH2</td>
<td>LUAD</td>
<td>ERK and FAK</td>
<td>[Chen et al., 2017a]</td>
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<tr>
<td>MicroRNA -29c</td>
<td>AKT2</td>
<td>RAC-beta serine/threonine-protein kinase</td>
<td>NSCLC</td>
<td>AKT and mTOR</td>
<td>[Sun et al., 2018]</td>
</tr>
<tr>
<td>MicroRNA -148</td>
<td>DNMT1</td>
<td>DNA (cytosine-5)-methyl transferase 1</td>
<td>NSCLC</td>
<td>-----------------------------</td>
<td>[Sui et al., 2015]</td>
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