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REVIEW

MicroRNAs in non-small cell lung cancer and idiopathic pulmonary fibrosis

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In spite of advances in the diagnosis and current molecular target therapies of lung cancer, this disease remains the most common cause of cancer-related death worldwide. Approximately 80% of lung cancers is non-small cell lung cancer (NSCLC), and 5-year survival rate of the disease is ~20%. On the other hand, idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown etiology. IPF is refractory to treatment and has a very low survival rate. Moreover, IPF is frequently associated with lung cancer. However, the common mechanisms shared by these two diseases remain poorly understood. In the post-genome sequence era, the discovery of noncoding RNAs, particularly microRNAs (miRNAs), has had a major impact on most biomedical fields, and these small molecules have been shown to contribute to the pathogenesis of NSCLC and IPF. Investigation of novel RNA networks mediated by miRNAs has improved our understanding of the molecular mechanisms of these diseases. This review summarizes our current knowledge on aberrantly expressed miRNAs regulating NSCLC and IPF based on miRNA expression signatures.
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INTRODUCTION

In spite of advances in diagnosis and current developing treatment, lung cancer remains the most common cause of cancer-related death worldwide, accounting for 1.59 million deaths in 2012.[1] Lung cancers are classified into two subtypes, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), according to the pathological features of the disease. NSCLC can be categorized into three histological subtypes according to the pathological characteristics: adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[2] The 2015 World Health Organization Classification of Lung Tumors was published last year as the fourth edition. In this edition, with certain drugs approved for specific subgroups of NSCLC patients, the decision of more exact histopathological subtyping is required. Recently, several therapeutic agents have been designed for the treatment of adenocarcinoma; these target epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements.[3–8] However, such a molecular-targeted treatment has not been yet approved for squamous cell carcinoma, large cell carcinoma and neuroendocrine cancer.[9–12]

Idiopathic pulmonary fibrosis (IPF) is a type of chronic progressive interstitial lung disease of unknown etiology. IPF is characterized by aberrant accumulation of extracellular matrix (ECM) proteins, activation of fibroblast proliferation and scarring of the lung epithelium.[13,14] IPF is associated with a very low survival rate, and effective treatment methods are limited.[15–17]

Many studies indicated that NSCLC and IPF share common risk factors.[14,18–21] In the clinical setting, NSCLC is often associated with IPF. Indeed, concurrent IPF was found in 7.5% of surgically resected lung cancer cases.[22] Furthermore, several reports have described a high incidence of lung cancer (4.4–13%) in patients with IPF.[23–25] These epidemiological studies linked the presence of IPF to the development of lung cancer. Moreover, the development of lung cancer in patients with IPF is markedly poorer prognosis.[26–28] Thus, these studies have shown that there are common pathogenic pathways activated in both lung cancer and IPF; investigation of the molecular pathogenesis of these diseases may lead to the development of new treatments for lung cancer and IPF.

BIOGENESIS AND FUNCTIONAL SIGNIFICANCE OF MICRORNAS

Post-genome sequence era, the discovery of noncoding RNAs in the human genome has provided a conceptual breakthrough in the investigation of molecular pathologies. Noncoding RNAs affect every stage of gene expression, from RNA transcription to RNA degradation.[29,30] Among the various types of noncoding RNAs, microRNAs (miRNAs) are small RNA molecules (18–25 nucleotides in length) that control the expression of protein-coding/non-protein-coding genes by repressing translation or degradation of RNA transcripts in a sequence-specific manner.[31–33] To date, the miRNA database (Release 21) contains 35 828 mature miRNA products in 223 species (http://www.mirbase.org/). With advancements in analytical

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methods, it is expected that the number of known miRNAs will continue to increase.

The miRNA-regulatory pathway involves a multistep process. First, miRNA genes are transcribed by RNA polymerase-II or -III using a gene-specific or shared promoter. Next, transcribed pri-miRNAs are modified by the double-stranded RNA-binding proteins DGCR8 and Drosha and processed to 60–100-nucleotide hairpin RNAs called pre-miRNAs.[34–36] Pre-miRNAs are then transported to the cytoplasm by exportin 5 and further processed by the endonucleases Dicer and TRBP into 19–22-nucleotide mature miRNAs.[34,35,37] Mature miRNA duplexes contain the mature miRNA (guide-strand miRNA) and the miRNA* (passenger-strand miRNA). This duplex is recruited to the RNA-induced silencing complex, which includes Ago2, a critical factor in the miRNA biogenesis pathway.[34,35]

In general, the guide-strand RNA from duplex miRNA is retained to direct recruitment of RNA-induced silencing complex to target mRNAs and repress RNA expression, whereas the passenger-strand RNA is degraded.[35,38] Several recent studies have shown that both guide and passenger strands of the miRNA duplex are functional in cancer cells.[39,40] Moreover, some miRNAs bind to the promoter region of the genes and activate the transcription of target genes.[33,41]

MIRNA EXPRESSION SIGNATURES IN NSCLC

Current advanced proteomic and genomic analyses lead to understanding the etiology of lung cancer.[42–45] Through basic genome analysis, several therapeutic agents have been designed—gefitinib, erlotinib and afatinib—which target epidermal growth factor receptor (*EGFR*), and crizotinib and alectinib, which targets the *EML4-ALK* fusion gene.[3,5–8]

To date, many reports have shown that a number of miRNAs contribute to lung cancer.[46–51] Expression levels of the *let-7* family were reduced in NSCLC tissues.[46] Overexpression of *let-7* suppresses the growth of cancer cells through targeting of RAS.[52]

Aberrantly expressed miRNAs disrupt the normally controlled RNA networks, and these events may trigger cancer cell initiation, development, metastasis and drug resistance.[33,53,54] Therefore, identification of dysregulated miRNAs in cancer cells is the pivotal step in the study of miRNA-mediated cancer networks. In this chapter, we focused on the downregulated miRNAs and described the functional significance of miRNAs and miRNA-regulated oncogenic genes in NSCLC and IPF. Upregulated miRNAs are described at length in other review articles. In this review, we describe four miRNA expression signatures of NSCLC clinical tissues from previous studies (Table 1a).

Among them, *miR-143* and *miR-145* form an miRNA cluster in the human chromosome 5q32 region and are frequently downregulated in several cancers, including lung cancer.[47,55–59] These miRNAs have been shown to function as tumor suppressors. The *p53* gene is a master of antitumor gene in the human genome and regulates a diverse set of anticancer cellular pathways.[60–62] The *p53* gene induces the expression of *miR-145* by direct binding to the *miR-145* promoter

Table 1a Differentially expressed miRNAs in NSCLC

Author	*Year*	*Sample*	*No. of tissues (normal/cancer)*	*Downregulated miRNAs*	*Upregulated miRNAs*	*Analysis platform*
Yanaihara[47]	2006	Clinical tissue	208 (104/104)	*miR-126*, miR-143, miR-192-prec, miR-224, miR-126, miR-30a-5p, miR-140, miR-9, miR-124a-1, miR-218-2, miR-95, miR-145, miR-198, miR-216-prec, miR-219-1, miR-125a-prec, miR-26a-1-prec, miR-199b-prec, let-7a-2-prec, miR-27b, miR-32, miR-29b-2, miR-220, miR-33, miR-181c-prec, miR-101-1, miR-124a-3, miR-125a*	*miR-21, miR-191, miR-210, miR-155, miR-205, miR-24-2, miR-212, miR-214, miR-17-3p, miR-106a, miR-197, miR-192, miR-146, miR-203, miR-150*	The microarray Chip (TJU version 1.1)
Gao[49]	2011	Clinical tissue	8 (4/4)	*miR-30a, miR-30d, miR-126, miR-652, miR-100, miR-143, miR-130a, miR-145, miR-30e, miR-126*, miR-181a, miR-125b, miR-886-3p, miR-451, miR-29c, miR-26b, miR-101, miR-320, miR-30b, miR-886-5p, miR-29a, miR-26a, miR-99a*	*miR-21, miR-31, miR-34a, miR-22*, miR-504, miR-18a, miR-412*	Exiqon A/S platform (Vedbaeck, Denmark)
Tan[50]	2011	Clinical tissue	68 (34/34)	*miR-30a, miR-388-3p, miR-195, miR-126, miR-138, miR-497, miR-125a-5p, miR-140-3p, miR-145, miR-486-5p*	*miR-205, miR-31, miR-203, miR-210, miR-182, miR-888, miR-429, miR-18b, miR-200b, miR-130b, miR-193b, miR-18a*	CapitalBio platform (CapitalBio Corp., Beijing, China)
Moriya[51]	2012	Clinical tissue	10 (5/5)	*miR-133a, miR-1247, miR-206, miR-99b*, miR-139-5p, miR-30a-3p, miR-138, miR-126, miR-30e-3p, miR-26a-1*, miR-140-3p, miR-34b, miR-574-3p, miR-628-5p, miR-186, miR-628-3p, miR-146b-5p, miR-16, miR-125a-5p, miR-320, miR-191*	Data not shown	TaqMan LDA Human miRNA Panel v2.0 (Applied Biosystems, Foster City, CA, USA)

Abbreviations: miRNA, microRNA; NSCLC, non-small cell lung cancer.

region.[63,64] *miR-145* has been shown to suppress the oncogenic c-*MYC* gene.[65–67] Interestingly, the *EGFR* and *Ras* oncogenes are therapeutic targets in lung cancers, and *miR-145* and *miR-143* have been shown to inhibit *EGFR* and *Ras* expression, respectively, in cancer cells.[59] Low expression of *miR-145* is associated with poor prognosis in NSCLC, and aberrant expression of *miR-145* mediates chemoresistance and brain metastasis.[67–69] Cisplatin is a key drug used to treat advanced NSCLCs, and *miR-145* is associated with the potential mechanism of cisplatin chemoresistance by regulation of CDK6.[70] In addition, downregulation of *miR-145* contributes to brain metastasis in NSCLC, which is associated with high mortality rates via upregulation of target genes, such as *OCT-4*, *EGFR*, *c-MYC*, *MUC-1* and *TPD52*.[67,71] Stromal expression of *miR-145-5p* also promotes neoangiogenesis in NSCLC development.[72]

Downregulation of *miR-126* has been reported in various cancers.[73–76] In the human genome, *miR-126* is mapped on chromosome 9q34.3 and within the intron of the epidermal growth factor-like domain 7 (*EGFL7*) gene. The *miR-126* host gene *EGFL7* has pivotal roles in angiogenesis and cancer cell progression and development.[77] The mature *miR-126* binds to the host gene *EGFL7*, resulting in a decrease in *EGFL7* expression; this creates a negative feedback loop.[78] Similar to *miR-126* downregulation in cancer cells, *miR-126** (*miR-126-5p*) expression has reduced in several types of cancer.[79] The sequence of mature *miR-126** is complementary to that of *miR-126*. Downregulation of *miR-126/miR-126** was reported in NSCLC.[80] Overexpression of *miR-126* inhibits the expression of vascular endothelial growth factor (*VEGF*)-*A* and impairs cancer cell growth.[75] VEGF enhances angiogenesis and upregulated VEGF-A in many cancers.[81] In miRNA biogenesis, the passenger strand of the miRNA is degraded; however, in the case of *miR-126/miR-126**, both miRNAs are stable and mediate characteristic functions. However, the role of *miR-126/miR-126** in the complex process of cancer formation remains largely unknown. The expression of *miR-126* is relatively low in SCLC, and *miR-126* functions as a negative regulator of SCLC cell growth.[82]

Downregulation of *miR-26* family members and the tumor-suppressive roles of these miRNAs have been reported in several cancers.[47,83] The *miR-26* family includes three subtypes in human

Table 1b Differentially expressed miRNAs in idiopathic pulmonary fibrosis

Author	*Year*	*Sample*	*No. of tissues (normal/IPF)*	*Downregulated miRNA*	*Upregulated miRNA*	*Analysis platform*
Pandit[103]	2010	Clinical tissue	20 (10/10)	*let-7d, miR-26a, miR-26b, miR-30a-5p,miR-30b, miR-30c, miR-30d, miR-30e-5p, miR-29c, miR-17-3p, miR-18a, miR-19a, miR-20a, miR-92*	Data not shown	8 × 15K Agilent human miRNA microarray containing 470 miRNAs (Sanger miRbase release 9.1)
Oak[124]	2011	Clinical tissue	19 (10/9) Normal/ rapidly progressive IPF	*miR-141, miR-101, miR-32, miR-19a, miR-19b, miR-142-3p, miR-423-3p, miR-144, miR-142-5p, miR-29b, miR-18a, miR-29c, miR-222, miR-30e, miR-130a, miR-30b, miR-15a, miR-140-5p, miR-96, miR-106b, miR-17, miR-223, miR-143, miR-20a, miR-27a, miR-126, miR-186, miR-29a, miR-22, miR-424, miR-30a, miR-103, miR-27b, miR-30c, let-7d, miR-181b*	*miR-423-5p, miR-155, miR-128, miR-374b, miR-21, miR-100, miR-125b, miR-140-3p, miR-125a-5p, miR-92a, let-7c*	RT2 miRNA PCR Array Human miFinder (SA Biosciences, Frederick, MD, USA)
Oak[124]	2011	Clinical tissue	16 (10/6) Normal/ slowly progressive IPF	*miR-141, miR-144, miR-32, miR-19a, miR-101, miR-130a, miR-19b, miR-142-5p, miR-142-3p, miR-18a, miR-106b, miR-143, miR-29c, miR-30b, miR-29b, miR-30e, miR-15a, miR-140-5p, miR-17, miR-20a, miR-22, miR-302c, miR-223, miR-222, miR-424, miR-103, miR-186, miR-29a, let-7d, miR-126, miR-376c, miR-93, miR-210, miR-181b*	*miR-155, miR-128, miR-125b, miR200c*	RT3 miRNA PCR Array Human miFinder (SA Biosciences)
Liang[85]	2014	Clinical tissue	169 (50/119)	*let-7a, let-7b, let-7c, let-7d, let-7g, miR-101, miR-103, miR-106a, miR-106b, miR-1271, miR-130a, miR-130b, miR-138, miR-141, miR-150, miR-15a, miR-15b, miR-17, miR-181b, miR-181c, miR-181d, miR-184, miR-18a, miR-191, miR-193b, miR-194, miR-197, miR-19a, miR-19b, miR-203, miR-205, miR-20a, miR-20b, miR-210, miR-22, miR-221, miR-222, miR-223, miR-23a, miR-24, miR-25, miR-26a, miR-27a, miR-29a, miR-29b, miR-29c, miR-30a, miR-30b, miR-30c, miR-30d, miR-30e, miR-320a, miR-320b, miR-320c, miR-320d, miR-335, miR-345, miR-375, miR-378, miR-422a, miR-425, miR-497, miR-500, miR-660, miR-663, miR-744, mi-92a miR-93*	*miR-205, miR-31, miR-34b, miR-376b, miR-376c, miR-382, miR-449a, miR-642, miR-100*	[HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array (transcript (gene) version)

Abbreviations: IPF, idiopathic pulmonary fibrosis; miRNA, microRNA.

cells: *miR-26a-1* (located on chromosome 3p22.2), *miR-26a-2* (located on chromosome 12q14.1) and *miR-26b* (located on chromosome 2q35). The seed sequences of these miRNAs are identical, suggesting that the *miR-26* family members regulate the same genes in human cells (miRBase, release 21; http://www.mirbase.org/). Ectopic expression of *miR-26a* in A549 cells inhibits the G_1–S transition and enhances cell death in response to CDDP (cisplatin) treatment.[84] In addition, high mobility group A2 (*HMGA2*) was previously investigated as a target of *miR-26a* in A549 cells.[85] *miR-26b* has been reported to exhibit anticancer functions in NSCLC cells through targeting *COX2* and *MIEN1*.[86] Another study showed that low expression of *miR-26b* was a risk factor for poor prognosis in patients with NSCLC.[87]

Downregulation of *miR-1* is frequently observed in many cancers, including lung cancer.[88] *miR-1* is highly conserved in the muscles of flies, mice and humans, and has been extensively investigated in various human diseases.[89] In human genome, *miR-1-1/miR-133a-2* (chromosome 20q13.33), *miR-1-2/miR-133a-1* (18q11.2) and *miR-206/miR-133b* (6p12.1) form clusters in three different chromosomal regions.[90] To investigate the functional roles of the *miR-1/miR-133a* cluster in cancer cells, we sequentially identified novel cancer pathways regulated by the *miR-1/miR-133a* cluster in several cancers, including NSCLC.[91] Restoration of both mature *miR-1* and *miR-133a* markedly inhibits cancer cell aggressiveness in NSCLC cells. In addition, the gene encoding coronin-1C is a common target of the *miR-1/miR-133a* cluster.[91] Activation of EGFR and MET oncogenic signaling enhances cancer cell aggressiveness and promotes lung cancer.[92] Overexpression of *miR-206* inhibits the dual signaling networks activated by MET and EGFR in lung squamous cell carcinoma cells.[93]

MIRNA EXPRESSION SIGNATURES IN IPF

IPF is a chronic fibrosing interstitial lung disease of unknown etiology.[14,16,94] One of the main characteristics of fibrosis is excess accumulation of ECM components, such as collagen, fibronectins, elastin and fibrillins.[95–97] Accumulated ECM components replace functional tissue and disrupt organ architecture. During the process of fibrosis development, several genes and pathways are activated. In particular, matrix metalloproteinases (MMPs) and connective tissue growth factor (CTGF) are upregulated in fibrotic lesions.[98–100] The activation of Wnt/β-catenin signaling regulates the expression of several pro-oncogenic molecules in cancer cells.[101] Activation of the Wnt/β-catenin pathway has reported in fibrotic disease, including IPF.[102] The Wnt pathway may also be activated by the fibrogenic cytokine transforming growth factor (TGF)-β.[99] Therefore, further studies are needed to investigate the regulation of the genes involved in these pathways by miRNAs.

The miRNA signature of human IPF lung specimens compared with controls has revealed the differential expression of 46 miRNAs.[103] Of these, *let-7d* was found to be abundantly expressed in normal lung epithelial cells and markedly reduced in IPF.[103] The expression level of *let-7d* was reduced by TGF-β, resulting in overexpression of its target gene *HMGA2* in IPF lesions.[104]

Expression of the *CTGF* gene is induced by TGF-β in a SMAD3/SMAD4-dependent manner, and CTGF enhances the synthesis of ECM proteins.[105–107] The downregulation of *miR-26a*, which targets *CTGF*, is involved in IPF pathogenesis, and *miR-26a* expression has been shown to be reduced by TGF-β.[100] In addition, studies have reported that CTGF expression is regulated by *miR-145*, *miR-30* and *miR-133*.[108]

Downregulation of *miR-18a*, *miR-19a* and *miR-19b*, members of the *miR-17-92* cluster, has also been reported in human IPF lung tissue.[109] The *miR-17-92* cluster is a proto-oncogenic cluster consisting of six miRNAs.[110,111] Recent studies have shown that *miR-18a*, *miR-19a* and *miR-19b* regulate CTGF in liver and cardiac fibrosis.[112,113]

The expression levels of *miR-21* and *miR-155* have also been shown to differ in lung tissues from patients with IPF and healthy controls (Table 1b). Upregulation of *miR-21* and *miR-155* has been reported by profiling of circulating serum miRNAs in patients with IPF and is associated with various clinical features of the disease.[114,115] Similar to the *miR-17-92* cluster, *miR-21* is regarded as an oncomiR in cancer cells.[116,117] Moreover, *miR-21* has been shown to have profibrotic activity in human IPF and murine bleomycin-induced lung fibrosis.[118] *miR-21* expression is induced by TGF-β and suppresses *smad-7*, a negative regulator of TGF-β signaling.[118] In addition, a recent study showed that *miR-155*-knockout mice are resistant to bleomycin-induced skin fibrosis.[119] Silencing of *miR-155* inhibits collagen synthesis function and blocks signaling through two profibrotic pathways, that is, the Wnt/β-catenin and Akt signaling pathways.[119]

ABERRANTLY EXPRESSED MIRNAS IN NSCLC AND IPF

Previous studies have shown that IPF and lung cancer share common risk factors, such as smoking, viral infection and chronic tissue injury.[14,18–20,120] These risk factors may lead to induction of critical genetic and epigenetic alterations in the human genome.[121] A previous study showed that p53 and p21 are upregulated in bronchial and alveolar epithelial cells in patients with IPF.[122] Moreover, constitutive chronic DNA damage may lead to mutation of the *p53* gene and could contribute to tumorigenesis in IPF.[123] Tumor-suppressor fragile histidine triad (*FHIT*) is a pivotal factor in lung cancer, and mutations in this gene have been detected in patients with IPF.[124] Using microsatellite DNA analysis, loss of heterozygosity was found in *MYCL1*, *FHIT*, *SPARC*, *p16Ink4* and *TP53* genomic loci in IPF.[125] Currently available sequence-based analyses may be used to identify genomic alterations common to lung cancer and IPF pathogenesis. Recent studies have indicated that constitutive chronic damage to the alveolar epithelium predisposes individuals to IPF and lung cancer.[126] During the process of repair and scar formation, alveolar epithelial cells undergo a transition to a mesenchymal phenotype, giving rise to fibroblasts and myofibroblasts.[126] Many studies have shown that TGF-β induces the epithelial–mesenchymal transition in alveolar epithelial cells.[126] Moreover, activation of TGF-β signaling and excessive accumulation of ECM proteins are observed in IPF and lung cancer, suggesting the presence of common molecular mechanisms in both diseases.[107,126,127] Thus, a large number of genes are commonly involved in the molecular pathogenesis of both diseases. Moreover, recent studies have demonstrated that miRNAs contribute to the pathogenesis of both NSCLC and IPF.[46,47,103,109,128] We focused on aberrantly expressed miRNAs in both diseases and elucidated the common molecular pathways based on miRNA expression signatures. miRNAs showing aberrant expression in lung cancer and IPF are shown in Tables 2a and 2b. For example, *miR-29* and *miR-30* are both downregulated in NSCLC and IPF. We will describe each of these miRNAs below.[129]

The *miR-29* family consists of three members (*miR-29a*, *miR-29b* and *miR-29c*) and forms clustered miRNA in human genome on different chromosome regions (*miR-29a* and *miR-29b-1* are 7q32, whereas *miR-29b-2* and *miR-29c* are 1q32).[130] Recent studies have shown that all members of *miR-29* family abnormally expressed in NCSLC and IPF.[47,85,103,131] The mechanisms regulating the expressions of *miR-29* family members have also been elucidated in previous studies.[132–134] Specifically, the promoter regions of *miR-29a* and

Table 2a miRNAs commonly downregulated in both NSCLC and IPF

No. of studies					
NSCLC	*IPF*	*Hsa-mature sequence*	*Stem–loop sequence*	*Locus*	*Clustered miRNA (within 10 kbp)*
1	4	*hsa-miR-29c-3p*	*hsa-mir-29c*	1q32.2	*hsa-miR-29b-2/hsa-miR-29c*
1	4	*hsa-miR-30b-5p*	*hsa-mir-30b*	8q24.22	*hsa-miR-30d/hsa-miR-30b*
1	4	*hsa-miR-30e-5p*	*hsa-mir-30e*	1p34.2	*hsa-miR-30e/hsa-miR-30c-1*
3	3	*hsa-miR-30a-5p*	*hsa-mir-30a*	6q13	—
2	3	*hsa-miR-101-3p*	*hsa-mir-101-1 hsa-mir-101-2*	1p31.3 9p24.1	*hsa-miR-101-1/hsa-miR-3671*
1	3	*hsa-miR-130a-3p*	*hsa-mir-130a*	11q12.1	—
1	3	*hsa-miR-29b-3p*	*hsa-mir-29b-1 hsa-mir-29b-2*	7q32.3 1q32.2	*hsa-miR-29b-1/hsa-miR-29a hsa-miR-29b-2/hsa-miR-29c*
2	2	*hsa-miR-143-3p*	*hsa-mir-143*	5q32	*hsa-miR-143 chr5/hsa-miR-145*
2	2	*hsa-miR-26a-5p*	*hsa-mir-26a-1 hsa-mir-26a-2*	3p22.2 12q14.1	—
1	2	*hsa-miR-140-5p*	*has-mir-140*	16q22.1	—
1	2	*hsa-miR-29a-3p*	*hsa-mir-29a*	7q32.3	*hsa-miR-29b-1 chr7/hsa-miR-29a*
1	2	*hsa-miR-30d-5p*	*hsa-mir-30d*	8q24.22	*hsa-miR-30d/hsa-miR-30b*
1	2	*hsa-miR-32-5p*	*hsa-mir-32*	9q31.3	—
1	2	*hsa-miR-320a*	*hsa-mir-320a*	8p21.3	—
4	1	*hsa-miR-126-3p*	*hsa-mir-126*	9q34.3	—
2	1	*hsa-miR-138-5p*	*hsa-mir-138-1 hsa-mir-138-2*	3p21.32 16q13	—
1	1	*hsa-let-7a-5p*	*hsa-let-7a-1 hsa-let-7a-2 hsa-let-7a-3*	9q22.32 11q24.1 22q13.31	*hsa-let-7a-1/hsa-let-7f-1/hsa-let-7d hsa-miR-100/hsa-let-7a-2 hsa-let-7a-3/hsa-miR-4763/hsa-let-7b*
1	1	*hsa-miR-181c-5p*	*hsa-mir-181c*	19p13.13	*hsa-miR-181c/hsa-miR-181d*
1	1	*hsa-miR-186-5p*	*hsa-mir-186*	1p31.1	—
1	1	*hsa-miR-191-5p*	*hsa-mir-191*	3p21.31	*hsa-miR-191/hsa-miR-425*
1	1	*hsa-miR-26b-5p*	*hsa-mir-26b*	2q35	—
1	1	*hsa-miR-27b-3p*	*hsa-mir-27b*	9q22.32	*hsa-miR-23b/hsa-miR-27b/hsa-miR-3074 /hsa-miR-24-1*
1	1	*hsa-miR-497-5p*	*hsa-mir-497*	17p13.1	*hsa-miR-497/hsa-miR-195*

Abbreviations: IPF, idiopathic pulmonary fibrosis; miRNA, microRNA; NSCLC, non-small cell lung cancer.

Table 2b miRNAs commonly upregulated in both NSCLC and IPF

No. of studies					
NSCLC	*IPF*	*Hsa-mature sequence*	*Stem–loop sequence*	*Locus*	*Clustered miRNA (within 10 kbp)*
1	2	*hsa-miR-155-5p*	*hsa-mir-155*	21q21.3	—
2	1	*hsa-miR-21-5p*	*hsa-mir-21*	17q23.2	—
2	1	*hsa-miR-205-5p*	*hsa-mir-205*	1q32.2	—
2	1	*hsa-miR-31-5p*	*hsa-mir-31*	9p21.3	—

Abbreviations: IPF, idiopathic pulmonary fibrosis; miRNA, microRNA; NSCLC, non-small cell lung cancer.

miR-29b-1 contain c-Myc and nuclear factor of kappaB (NF-κB)-binding sites, and the expression of *miR-29* family members can be repressed by c-Myc and NF-κB.[135] A previous study showed that low expression of *miR-29b* is more common in NSCLC, exhibiting high c-Myc expression.[136] Moreover, high c-Myc expression in NSCLC is associated with low *miR-29b* expression and shorter survival durations than those in patients with low c-Myc expression (and high *miR-29b* expression).[136] The expression of *miR-29* family is suppressed by growth factors or cytokines, such as the TGF-β/Smad pathway. Interestingly, researchers have demonstrated the presence of a regulatory loop feedback between TGF-β and the *miR-29* family.[130] The *miR-29* family involves in multiple profibrotic and inflammatory pathways, and its expression is markedly reduced in fibrotic lungs.[103,109,131] In addition, members of the *miR-29* family inhibit TGF-β-induced ECM synthesis through activation of the phosphoinositol 3-kinase/AKT pathway in human lung fibroblasts.[133] According to previous studies, members of the *miR-29* family inhibits antifibrotic activity through regulation of the ECM and epithelial–mesenchymal transition involved genes.[134] Moreover, in the initial stage of fibrosis, inflammatory cytokines inhibit the expression of *miR-29* family members in fibroblasts or myofibroblasts, subsequently resulting in decreased *miR-29* family members, which enhances the expression of collagens and ECM-related genes that are associated with the development of IPF.[134]

The expression levels of *miR-29* family members are also downregulated in lung cancer and various types of cancer.[47,137,138] Indeed,

miR-29 family members regulate several common pathways involved in carcinogenesis and cancer progression and act as antitumor miRNAs in many types of cancer.[130,139,140] We demonstrated that *miR-29* family members exert antitumor effects by directly targeting lysyl oxidase-like protein 2, which modifies ECM components and promotes cancer progression.[141] The *miR-29* family is an important regulator of the ECM and epithelial–mesenchymal transition, which are both involved in the pathogenesis of IPF and progression of lung cancer. The relationship between IPF and lung cancer still remains unclear; however, studying common molecular pathways regulated by *miR-29* family members may lead to the elucidation of common pathogenic pathways involved in the development of both diseases.

The *miR-30* family has five isoforms (*miR-30a*, *miR-30b*, *miR-30c*, *miR-30d* and *miR-30e*); *miR-30a* and *miR-30c* are located on chromosome 6q13, *miR-30b* and *miR-30d* are located on chromosome 8q24.22, and *miR-30e* is located on chromosome 1p34.2. (Entrez Gene, http://www.ncbi.nlm.nih.gov/gene/, accessed 4 April 2016). These miRNAs are involved in various types of cancer, including breast cancer, glioma, osteoblastic tumor and pancreatic cancer.[142–145] In lung cancer, *miR-30b* and *miR-30c* inhibit NSCLC cell proliferation by targeting *Rab18*, which belongs to the *RAS* superfamily.[146] The expression of *miR-30* family was reduced in lung cancer tissues and caused the dysregulation of *MMP19* expression.[147] Profibrotic mediator *WISP1* (WNT1-inducible signaling pathway protein 1) is upregulated in IPF tissues.[99,102] *WISP1* is associated with the epithelial–mesenchymal transition in alveolar epithelial type II (ATII) cells and ECM synthesis by fibroblasts.[148] Alterations in *miR-30a* expression reverse TGF-β1-induced expression of *WISP1* in lung fibroblasts, including experimental lung fibrosis and primary IPF fibroblasts.[149] Activation of *WISP1* signaling may result in various pathologies, including fibrosis and cancer.

CONCLUSIONS

IPF and lung cancer may share a similar etiology and that there may be a common course contributing to the development of lung cancer and IPF in this context. Various signals and molecules transmit individual signaling pathways, and the general pathway can converge and may promote inflammatory processes in IPF and cancer development. These phenomena may lead to a high incidence of complications in lung cancer and IPF. Consequently, attempts have been made to develop effective treatment strategies for both diseases, including the use of tyrosine kinase receptor inhibitors, such as nintedanib,[150] which was initially developed for the treatment of cancer and has recently been approved for the treatment of IPF. In this review, we highlight the miRNA-mediated pathways and molecules that can be associated with both of these diseases. However, there are still several unresolved questions regarding the possible links between lung cancer and IPF. For example, how do diffuse fibrotic lesions confer local development of lung cancer? Furthermore, the mechanistic possibilities discussed here have mostly been generated in the study of cultured cells *in vitro*. We believe that a better understanding of the detailed mechanisms linking IPF and lung cancer will lead to identification of novel therapeutic targets and new therapies for the prevention of cancer development.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Stewart, B. W. & Wild, C. P. *World Cancer Report 2014* (International Agency for Research on Cancer, Lyon, France, 2014).
2 Hori, M., Matsuda, T., Shibata, A., Katanoda, K., Sobue, T., Nishimoto, H. *et al.* Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn. J. Clin. Oncol.* **45**, 884–891 (2015).
3 Paez, J. G., Jänne, P. A., Lee, J. C., Tracy, S., Greulich, H., Gabriel, S. *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**, 1497–1500 (2004).
4 Lynch, T. J., Bell, D. W., Sordella, R., Gurubhagavatula, S., Okimoto, R. A., Brannigan, B. W. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **350**, 2129–2139 (2004).
5 Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E. *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* **13**, 239–246 (2012).
6 Wu, Y.-L., Zhou, C., Hu, C.-P., Feng, J., Lu, S., Huang, Y. *et al.* Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* **15**, 213–222 (2014).
7 Shaw, A. T., Kim, D. W., Nakagawa, K., Seto, T., Crino, L., Ahn, M. J. *et al.* Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N. Engl. J. Med.* **368**, 2385–2394 (2013).
8 Gadgeel, S. M., Gandhi, L., Riely, G. J., Chiappori, A. A., West, H. L., Azada, M. C. *et al.* Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol.* **15**, 1119–1128 (2014).
9 Rekhtman, N., Paik, P. K., Arcila, M. E., Tafe, L. J., Oxnard, G. R., Moreira, A. L. *et al.* Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. *Clin. Cancer Res.* **18**, 1167–1176 (2012).
10 Forbes, S. A., Bhamra, G., Bamford, S., Dawson, E., Kok, C., Clements, J. *et al.* The catalogue of somatic mutations in cancer (COSMIC). *Curr. Protoc. Hum. Genet.* **Chapter 10** (Unit 10), 11 (2008).
11 Paik, P. K., Varghese, A. M., Sima, C. S., Moreira, A. L., Ladanyi, M., Kris, M. G. *et al.* Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. *Mol. Cancer Ther.* **11**, 2535–2540 (2012).
12 Shaw, A. T. & Solomon, B. J. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* **372**, 683–684 (2015).
13 Allen, J. T. & Spiteri, M. A. Growth factors in idiopathic pulmonary fibrosis: relative roles. *Respir. Res.* **3**, 13 (2002).
14 King, T. E. Jr., Pardo, A. & Selman, M. Idiopathic pulmonary fibrosis. *Lancet* **378**, 1949–1961 (2011).
15 Bjoraker, J. A., Ryu, J. H., Edwin, M. K., Myers, J. L., Tazelaar, H. D., Schroeder, D. R. *et al.* Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **157**, 199–203 (1998).
16 Gross, T. J. & Hunninghake, G. W. Idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **345**, 517–525 (2001).
17 Ley, B., Collard, H. R. & King, T. E. Jr Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **183**, 431–440 (2011).
18 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am. J. Respir. Crit. Care Med.* **161**, 646–664 (2000).
19 Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K. *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* **183**, 788–824 (2011).
20 Pope, III C., Burnett, R. T., Thun, M. J., Calle, E. E., Krewski, D., Ito, K. *et al.* Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* **287**, 1132–1141 (2002).
21 Reck, M., Heigener, D. F., Mok, T., Soria, J.-C. & Rabe, K. F. Management of non-small-cell lung cancer: recent developments. *Lancet* **382**, 709–719 (2013).
22 Kawasaki, H., Nagai, K., Yokose, T., Yoshida, J., Nishimura, M., Takahashi, K. *et al.* Clinicopathological characteristics of surgically resected lung cancer associated with idiopathic pulmonary fibrosis. *J. Surg. Oncol.* **76**, 53–57 (2001).
23 Hubbard, R., Venn, A., Lewis, S. & Britton, J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am. J. Respir. Crit. Care Med.* **161**, 5–8 (2000).
24 Turner-Warwick, M., Lebowitz, M., Burrows, B. & Johnson, A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* **35**, 496–499 (1980).
25 Tomassetti, S., Gurioli, C., Ryu, J. H., Decker, P. A., Ravaglia, C., Tantalocco, P. *et al.* The impact of lung cancer on survival of idiopathic pulmonary fibrosis. *Chest* **147**, 157–164 (2015).
26 Kumar, P., Goldstraw, P., Yamada, K., Nicholson, A. G., Wells, A. U., Hansell, D. M. *et al.* Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. *J. Thorac. Cardiovasc. Surg.* **125**, 1321–1327 (2003).

27 Watanabe, A., Higami, T., Ohori, S., Koyanagi, T., Nakashima, S. & Mawatari, T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? *J. Thorac. Cardiovasc. Surg.* **136**, e1351–e1352 (2008).
28 Saito, Y., Kawai, Y., Takahashi, N., Ikeya, T., Murai, K., Kawabata, Y. *et al.* Survival after surgery for pathologic stage IA non-small cell lung cancer associated with idiopathic pulmonary fibrosis. *Ann. Thorac. Surg.* **92**, 1812–1817 (2011).
29 Shabalina, S. A. & Spiridonov, N. A. The mammalian transcriptome and the function of non-coding DNA sequences. *Genome Biol.* **5**, 105 (2004).
30 Lindberg, J. & Lundeberg, J. The plasticity of the mammalian transcriptome. *Genomics* **95**, 1–6 (2010).
31 Bartel, D. P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116**, 281–297 (2004).
32 Filipowicz, W., Bhattacharyya, S. N. & Sonenberg, N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat. Rev. Genet.* **9**, 102–114 (2008).
33 Esquela-Kerscher, A. & Slack, F. J. Oncomirs - microRNAs with a role in cancer. *Nat. Rev. Cancer* **6**, 259–269 (2006).
34 Gregory, R. I. & Shiekhattar, R. MicroRNA biogenesis and cancer. *Cancer Res.* **65**, 3509–3512 (2005).
35 Goto, Y., Kurozumi, A., Enokida, H., Ichikawa, T. & Seki, N. Functional significance of aberrantly expressed microRNAs in prostate cancer. *Int. J. Urol.* **22**, 242–252 (2015).
36 Nguyen, T. A., Jo, M. H., Choi, Y. G., Park, J., Kwon, S. C., Hohng, S. *et al.* Functional anatomy of the human microprocessor. *Cell* **161**, 1374–1387 (2015).
37 Wilson, R. C., Tambe, A., Kidwell, M. A., Noland, C. L., Schneider, C. P. & Doudna, J. A. Dicer-TRBP complex formation ensures accurate mammalian microRNA biogenesis. *Mol. Cell* **57**, 397–407 (2015).
38 Matranga, C., Tomari, Y., Shin, C., Bartel, D. P. & Zamore, P. D. Passenger-strand cleavage facilitates assembly of siRNA into Ago2-containing RNAi enzyme complexes. *Cell* **123**, 607–620 (2005).
39 Matsushita, R., Seki, N., Chiyomaru, T., Inoguchi, S., Ishihara, T., Goto, Y. *et al.* Tumour-suppressive microRNA-144-5p directly targets CCNE1/2 as potential prognostic markers in bladder cancer. *Br. J. Cancer* **113**, 282–289 (2015).
40 Matsushita, R., Yoshino, H., Enokida, H., Goto, Y., Miyamoto, K., Yonemori, M. *et al.* Regulation of UHRF1 by dual-strand tumor-suppressor microRNA-145 (miR-145-5p and miR-145-3p): inhibition of bladder cancer cell aggressiveness. *Oncotarget* (e-pub ahead of print 9 April 2016; doi:10.18632/oncotarget.8668).
41 Lytle, J. R., Yario, T. A. & Steitz, J. A. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. *Proc. Natl Acad. Sci. USA* **104**, 9667–9672 (2007).
42 Cancer Genome Atlas Research N., Weinstein, J. N., Collisson, E. A., Mills, G. B., Shaw, K. R., Ozenberger, B. A. *et al.* The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* **45**, 1113–1120 (2013).
43 Vogelstein, B., Papadopoulos, N., Velculescu, V. E., Zhou, S., Diaz, L. A. & Kinzler, K. W. Cancer genome landscapes. *Science (New York, NY)* **339**, 1546–1558 (2013).
44 Cooper, W. A., Lam, D. C., O'Toole, S. A. & Minna, J. D. Molecular biology of lung cancer. *J. Thorac. Dis.* **5** (Suppl 5), S479–S490 (2013).
45 Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* **511**, 543–550 (2014).
46 Takamizawa, J., Konishi, H., Yanagisawa, K., Tomida, S., Osada, H., Endoh, H. *et al.* Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res.* **64**, 3753–3756 (2004).
47 Yanaihara, N., Caplen, N., Bowman, E., Seike, M., Kumamoto, K., Yi, M. *et al.* Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. *Cancer Cell* **9**, 189–198 (2006).
48 Hu, Z., Chen, J., Tian, T., Zhou, X., Gu, H., Xu, L. *et al.* Genetic variants of miRNA sequences and non-small cell lung cancer survival. *J. Clin. Invest.* **118**, 2600–2608 (2008).
49 Gao, W., Shen, H., Liu, L., Xu, J., Xu, J. & Shu, Y. MiR-21 overexpression in human primary squamous cell lung carcinoma is associated with poor patient prognosis. *J. Cancer Res. Clin. Oncol.* **137**, 557–566 (2011).
50 Tan, X., Qin, W., Zhang, L., Hang, J., Li, B., Zhang, C. *et al.* A 5-microRNA signature for lung squamous cell carcinoma diagnosis and hsa-miR-31 for prognosis. *Clin. Cancer Res.* **17**, 6802–6811 (2011).
51 Moriya, Y., Nohata, N., Kinoshita, T., Mutallip, M., Okamoto, T., Yoshida, S. *et al.* Tumor suppressive microRNA-133a regulates novel molecular networks in lung squamous cell carcinoma. *J. Hum. Genet.* **57**, 38–45 (2012).
52 Johnson, S. M., Grosshans, H., Shingara, J., Byrom, M., Jarvis, R., Cheng, A. *et al.* RAS is regulated by the let-7 microRNA family. *Cell* **120**, 635–647 (2005).
53 Volinia, S., Calin, G. A., Liu, C. G., Ambs, S., Cimmino, A., Petrocca, F. *et al.* A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc. Natl Acad. Sci. USA* **103**, 2257–2261 (2006).
54 Di Leva, G., Garofalo, M. & Croce, C. M. MicroRNAs in cancer. *Annu. Rev. Pathol.* **9**, 287–314 (2014).
55 Michael, M. Z., O' Connor, S. M., van Holst Pellekaan, N. G., Young, G. P. & James, R. J. Reduced accumulation of specific microRNAs in colorectal neoplasia. *Mol. Cancer Res.* **1**, 882–891 (2003).
56 Slaby, O., Svoboda, M., Fabian, P., Smerdova, T., Knoflickova, D., Bednarikova, M. *et al.* Altered expression of miR-21, miR-31, miR-143 and miR-145 is related to clinicopathologic features of colorectal cancer. *Oncology.* **72**, 397–402 (2007).
57 Chiyomaru, T., Enokida, H., Tatarano, S., Kawahara, K., Uchida, Y., Nishiyama, K. *et al.* miR-145 and miR-133a function as tumour suppressors and directly regulate FSCN1 expression in bladder cancer. *Br. J. Cancer* **102**, 883–891 (2010).
58 Wu, B. L., Xu, L. Y., Du, Z. P., Liao, L. D., Zhang, H. F., Huang, Q. *et al.* MiRNA profile in esophageal squamous cell carcinoma: downregulation of miR-143 and miR-145. *World J. Gastroenterol.* **17**, 79–88 (2011).
59 Zhu, H., Dougherty, U., Robinson, V., Mustafi, R., Pekow, J., Kupfer, S. *et al.* EGFR signals downregulate tumor suppressors miR-143 and miR-145 in Western diet-promoted murine colon cancer: role of G1 regulators. *Mol. Cancer Res.* **9**, 960–975 (2011).
60 el-Deiry, W. S., Tokino, T., Velculescu, V. E., Levy, D. B., Parsons, R., Trent, J. M. *et al.* WAF1, a potential mediator of p53 tumor suppression. *Cell* **75**, 817–825 (1993).
61 Sigal, A. & Rotter, V. Oncogenic mutations of the p53 tumor suppressor: the demons of the guardian of the genome. *Cancer Res.* **60**, 6788–6793 (2000).
62 Luo, J., Manning, B. D. & Cantley, L. C. Targeting the PI3K-Akt pathway in human cancer: rationale and promise. *Cancer Cell* **4**, 257–262 (2003).
63 Suzuki, H. I., Yamagata, K., Sugimoto, K., Iwamoto, T., Kato, S. & Miyazono, K. Modulation of microRNA processing by p53. *Nature* **460**, 529–533 (2009).
64 Boominathan, L. The tumor suppressors p53, p63, and p73 are regulators of microRNA processing complex. *PLoS ONE* **5**, e10615 (2010).
65 Sachdeva, M., Zhu, S., Wu, F., Wu, H., Walia, V., Kumar, S. *et al.* p53 represses c-Myc through induction of the tumor suppressor miR-145. *Proc. Natl Acad. Sci. USA* **106**, 3207–3212 (2009).
66 Chen, Z., Zeng, H., Guo, Y., Liu, P., Pan, H., Deng, A. *et al.* miRNA-145 inhibits non-small cell lung cancer cell proliferation by targeting c-Myc. *J. Exp. Clin. Cancer Res.* **29**, 151 (2010).
67 Donzelli, S., Mori, F., Bellissimo, T., Sacconi, A., Casini, B., Frixa, T. *et al.* Epigenetic silencing of miR-145-5p contributes to brain metastasis. *Oncotarget* **6**, 35183–35201 (2015).
68 Campayo, M., Navarro, A., Vinolas, N., Diaz, T., Tejero, R., Gimferrer, J. M. *et al.* Low miR-145 and high miR-367 are associated with unfavourable prognosis in resected nonsmall cell lung cancer. *Eur. Respir. J.* **41**, 1172–1178 (2013).
69 Shen, H., Shen, J., Wang, L., Shi, Z., Wang, M., Jiang, B. H. *et al.* Low miR-145 expression level is associated with poor pathological differentiation and poor prognosis in non-small cell lung cancer. *Biomed. Pharmacother.* **69**, 301–305 (2015).
70 Bar, J., Gorn-Hondermann, I., Moretto, P., Perkins, T. J., Niknejad, N., Stewart, D. J. *et al.* miR profiling identifies cyclin-dependent kinase 6 downregulation as a potential mechanism of acquired cisplatin resistance in non-small-cell lung carcinoma. *Clin. Lung Cancer.* **16**, e121–e129 (2015).
71 Zhao, C., Xu, Y., Zhang, Y., Tan, W., Xue, J., Yang, Z. *et al.* Downregulation of miR-145 contributes to lung adenocarcinoma cell growth to form brain metastases. *Oncol. Rep.* **30**, 2027–2034 (2013).
72 Dimitrova, N., Gocheva, V., Bhutkar, A., Resnick, R., Jong, R. M., Miller, K. M. *et al.* Stromal expression of miR-143/145 promotes neoangiogenesis in lung cancer development. *Cancer Discov.* **6**, 188–201 (2016).
73 Guo, C., Sah, J. F., Beard, L., Willson, J. K., Markowitz, S. D. & Guda, K. The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. *Genes Chromosomes Cancer* **47**, 939–946 (2008).
74 Tavazoie, S. F., Alarcon, C., Oskarsson, T., Padua, D., Wang, Q., Bos, P. D. *et al.* Endogenous human microRNAs that suppress breast cancer metastasis. *Nature* **451**, 147–152 (2008).
75 Liu, B., Peng, X. C., Zheng, X. L., Wang, J. & Qin, Y. W. MiR-126 restoration down-regulate VEGF and inhibit the growth of lung cancer cell lines *in vitro* and *in vivo*. *Lung Cancer* **66**, 169–175 (2009).
76 Feng, R., Chen, X., Yu, Y., Su, L., Yu, B., Li, J. *et al.* miR-126 functions as a tumour suppressor in human gastric cancer. *Cancer Lett.* **298**, 50–63 (2010).
77 Saito, Y., Friedman, J. M., Chihara, Y., Egger, G., Chuang, J. C. & Liang, G. Epigenetic therapy upregulates the tumor suppressor microRNA-126 and its host gene EGFL7 in human cancer cells. *Biochem. Biophys. Res. Commun.* **379**, 726–731 (2009).
78 Sun, Y., Bai, Y., Zhang, F., Wang, Y., Guo, Y. & Guo, L. miR-126 inhibits non-small cell lung cancer cells proliferation by targeting EGFL7. *Biochem. Biophys. Res. Commun.* **391**, 1483–1489 (2010).
79 Meister, J. & Schmidt, M. H. miR-126 and miR-126*: new players in cancer. *Scientific World Journal* **10**, 2090–2100 (2010).
80 Cho, W. C., Chow, A. S. & Au, J. S. Restoration of tumour suppressor hsa-miR-145 inhibits cancer cell growth in lung adenocarcinoma patients with epidermal growth factor receptor mutation. *Eur. J. Cancer* **45**, 2197–2206 (2009).
81 Ferrara, N., Gerber, H.-P. & LeCouter, J. The biology of VEGF and its receptors. *Nat. Med.* **9**, 669–676 (2003).
82 Miko, E., Margitai, Z., Czimmerer, Z., Varkonyi, I., Dezso, B., Lanyi, A. *et al.* miR-126 inhibits proliferation of small cell lung cancer cells by targeting SLC7A5. *FEBS Lett.* **585**, 1191–1196 (2011).
83 Dalmay, T. & Edwards, D. R. MicroRNAs and the hallmarks of cancer. *Oncogene* **25**, 6170–6175 (2006).
84 Yang, Y., Zhang, P., Zhao, Y., Yang, J., Jiang, G. & Fan, J. Decreased MicroRNA-26a expression causes cisplatin resistance in human non-small cell lung cancer. *Cancer Biol. Ther.* **17**, 515–525 (2016).
85 Liang, H., Gu, Y., Li, T., Zhang, Y., Huangfu, L., Hu, M. *et al.* Integrated analyses identify the involvement of microRNA-26a in epithelial-mesenchymal transition during idiopathic pulmonary fibrosis. *Cell Death Dis.* **5**, e1238 (2014).
86 Li, D., Wei, Y., Wang, D., Gao, H. & Liu, K. MicroRNA-26b suppresses the metastasis of non-small cell lung cancer by targeting MIEN1 via NF-kappaB/MMP-9/VEGF pathways. *Biochem. Biophys. Res. Commun.* **472**, 465–470 (2016).

87 Jiang, L. P., Zhu, Z. T. & He, C. Y. Expression of miRNA-26b in the diagnosis and prognosis of patients with non-small-cell lung cancer. *Future Oncol.* **12**, 1105–1115 (2016).
88 Nasser, M. W., Datta, J., Nuovo, G., Kutay, H., Motiwala, T., Majumder, S. *et al.* Down-regulation of micro-RNA-1 (miR-1) in lung cancer. Suppression of tumorigenic property of lung cancer cells and their sensitization to doxorubicin-induced apoptosis by miR-1. *J. Biol. Chem.* **283**, 33394–33405 (2008).
89 Qian, L., Wythe, J. D., Liu, J., Cartry, J., Vogler, G., Mohapatra, B. *et al.* Tinman/Nkx2-5 acts via miR-1 and upstream of Cdc42 to regulate heart function across species. *J. Cell Biol.* **193**, 1181–1196 (2011).
90 Nohata, N., Sone, Y., Hanazawa, T., Fuse, M., Kikkawa, N., Yoshino, H. *et al.* miR-1 as a tumor suppressive microRNA targeting TAGLN2 in head and neck squamous cell carcinoma. *Oncotarget* **2**, 29–42 (2011).
91 Mataki, H., Enokida, H., Chiyomaru, T., Mizuno, K., Matsushita, R., Goto, Y. *et al.* Downregulation of the microRNA-1/133a cluster enhances cancer cell migration and invasion in lung-squamous cell carcinoma via regulation of Coronin1C. *J. Hum. Genet.* **60**, 53–61 (2015).
92 Rikova, K., Guo, A., Zeng, Q., Possemato, A., Yu, J., Haack, H. *et al.* Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* **131**, 1190–1203 (2007).
93 Mataki, H., Seki, N., Chiyomaru, T., Enokida, H., Goto, Y., Kumamoto, T. *et al.* Tumor-suppressive microRNA-206 as a dual inhibitor of MET and EGFR oncogenic signaling in lung squamous cell carcinoma. *Int. J. Oncol.* **46**, 1039–1050 (2015).
94 Katzenstein, A.-L. & Myers, J. Idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **157**, 1301–1315 (1998).
95 Antoniades, H. N., Bravo, M. A., Avila, R. E., Galanopoulos, T., Neville-Golden, J., Maxwell, M. *et al.* Platelet-derived growth factor in idiopathic pulmonary fibrosis. *J. Clin. Invest.* **86**, 1055–1064 (1990).
96 Thannickal, V. J., Toews, G. B., White, E. S., Lynch, J. P. 3rd & Martinez, F. J. Mechanisms of pulmonary fibrosis. *Annu. Rev. Med.* **55**, 395–417 (2004).
97 Kim, K. K., Kugler, M. C., Wolters, P. J., Robillard, L., Galvez, M. G., Brumwell, A. N. *et al.* Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. *Proc. Natl Acad. Sci. USA* **103**, 13180–13185 (2006).
98 Suga, M., Iyonaga, K., Okamoto, T., Gushima, Y., Miyakawa, H., Akaike, T. *et al.* Characteristic elevation of matrix metalloproteinase activity in idiopathic interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* **162**, 1949–1956 (2000).
99 Chilosi, M., Poletti, V., Zamo, A., Lestani, M., Montagna, L., Piccoli, P. *et al.* Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. *Am. J. Pathol.* **162**, 1495–1502 (2003).
100 Liang, H., Xu, C., Pan, Z., Zhang, Y., Xu, Z., Chen, Y. *et al.* The antifibrotic effects and mechanisms of microRNA-26a action in idiopathic pulmonary fibrosis. *Mol. Ther.* **22**, 1122–1133 (2014).
101 Stewart, D. J. WNT signaling pathway in non-small cell lung cancer. *J. Natl Cancer Inst.* **106**, djt356 (2014).
102 Konigshoff, M., Balsara, N., Pfaff, E. M., Kramer, M., Chrobak, I., Seeger, W. *et al.* Functional Wnt signaling is increased in idiopathic pulmonary fibrosis. *PLoS ONE* **3**, e2142 (2008).
103 Pandit, K. V., Corcoran, D., Yousef, H., Yarlagadda, M., Tzouvelekis, A., Gibson, K. F. *et al.* Inhibition and role of let-7d in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **182**, 220–229 (2010).
104 Huleihel, L., Ben-Yehudah, A., Milosevic, J., Yu, G., Pandit, K., Sakamoto, K. *et al.* Let-7d microRNA affects mesenchymal phenotypic properties of lung fibroblasts. *Am. J. Physiol. Lung Cell Mol. Physiol.* **306**, L534–L542 (2014).
105 Holmes, A., Abraham, D. J., Sa, S., Shiwen, X., Black, C. M. & Leask, A. CTGF and SMADs, maintenance of scleroderma phenotype is independent of SMAD signaling. *J. Biol. Chem.* **276**, 10594–10601 (2001).
106 Blom, I. E., Goldschmeding, R. & Leask, A. Gene regulation of connective tissue growth factor: new targets for antifibrotic therapy? *Matrix Biol.* **21**, 473–482 (2002).
107 Leask, A. & Abraham, D. J. TGF-beta signaling and the fibrotic response. *FASEB J.* **18**, 816–827 (2004).
108 Duisters, R. F., Tijsen, A. J., Schroen, B., Leenders, J. J., Lentink, V., van der Made, I. *et al.* miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ. Res.* **104**, 170–178 (2009).
109 Pandit, K. V., Milosevic, J. & Kaminski, N. MicroRNAs in idiopathic pulmonary fibrosis. *Transl. Res.* **157**, 191–199 (2011).
110 Tanzer, A. & Stadler, P. F. Molecular evolution of a microRNA cluster. *J. Mol. Biol.* **339**, 327–335 (2004).
111 Mendell, J. T. miRiad roles for the miR-17-92 cluster in development and disease. *Cell* **133**, 217–222 (2008).
112 Kodama, T., Takehara, T., Hikita, H., Shimizu, S., Shigekawa, M., Tsunematsu, H. *et al.* Increases in p53 expression induce CTGF synthesis by mouse and human hepatocytes and result in liver fibrosis in mice. *J. Clin. Invest.* **121**, 3343–3356 (2011).
113 van Almen, G. C., Verhesen, W., van Leeuwen, R. E., van de Vrie, M., Eurlings, C., Schellings, M. W. *et al.* MicroRNA-18 and microRNA-19 regulate CTGF and TSP-1 expression in age-related heart failure. *Aging Cell* **10**, 769–779 (2011).
114 Li, P., Li, J., Chen, T., Wang, H., Chu, H., Chang, J. *et al.* Expression analysis of serum microRNAs in idiopathic pulmonary fibrosis. *Int. J. Mol. Med.* **33**, 1554–1562 (2014).
115 Li, P., Zhao, G. Q., Chen, T. F., Chang, J. X., Wang, H. Q., Chen, S. S. *et al.* Serum miR-21 and miR-155 expression in idiopathic pulmonary fibrosis. *J. Asthma* **50**, 960–964 (2013).
116 Krichevsky, A. M. & Gabriely, G. miR-21: a small multi-faceted RNA. *J. Cell Mol. Med.* **13**, 39–53 (2009).
117 Cho, W. C. OncomiRs: the discovery and progress of microRNAs in cancers. *Mol. Cancer* **6**, 60 (2007).
118 Liu, G., Friggeri, A., Yang, Y., Milosevic, J., Ding, Q., Thannickal, V. J. *et al.* miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. *J. Exp. Med.* **207**, 1589–1597 (2010).
119 Yan, Q., Chen, J., Li, W., Bao, C. & Fu, Q. Targeting miR-155 to treat experimental scleroderma. *Sci. Rep.* **6**, 20314 (2016).
120 Reck, M., Heigener, D. F., Mok, T., Soria, J. C. & Rabe, K. F. Management of non-small-cell lung cancer: recent developments. *Lancet* **382**, 709–719 (2013).
121 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am. J. Respir. Crit. Care Med.* **161**, 646–664 (2000).
122 Vancheri, C., Failla, M., Crimi, N. & Raghu, G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. *Eur. Respir. J.* **35**, 496–504 (2010).
123 Kuwano, K., Kunitake, R., Kawasaki, M., Nomoto, Y., Hagimoto, N., Nakanishi, Y. *et al.* P21Waf1/Cip1/Sdi1 and p53 expression in association with DNA strand breaks in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **154**, 477–483 (1996).
124 Hojo, S., Fujita, J., Yamadori, I., Kamei, T., Yoshinouchi, T., Ohtsuki, Y. *et al.* Heterogeneous point mutations of the p53 gene in pulmonary fibrosis. *Eur. Respir. J.* **12**, 1404–1408 (1998).
125 Uematsu, K., Yoshimura, A., Gemma, A., Mochimaru, H., Hosoya, Y., Kunugi, S. *et al.* Aberrations in the fragile histidine triad (FHIT) gene in idiopathic pulmonary fibrosis. *Cancer Res.* **61**, 8527–8533 (2001).
126 Demopoulos, K., Arvanitis, D. A., Vassilakis, D. A., Siafakas, N. M. & Spandidos, D. A. MYCL1, FHIT, SPARC, p16(INK4) and TP53 genes associated to lung cancer in idiopathic pulmonary fibrosis. *J. Cell. Mol. Med.* **6**, 215–222 (2002).
127 Willis, B. C. & Borok, Z. TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease. *Am. J. Physiol. Lung Cell Mol. Physiol.* **293**, L525–L534 (2007).
128 Bhowmick, N. A., Neilson, E. G. & Moses, H. L. Stromal fibroblasts in cancer initiation and progression. *Nature* **432**, 332–337 (2004).
129 Yu, S. L., Chen, H. Y., Chang, G. C., Chen, C. Y., Chen, H. W., Singh, S. *et al.* MicroRNA signature predicts survival and relapse in lung cancer. *Cancer Cell* **13**, 48–57 (2008).
130 Wang, Y., Zhang, X., Li, H., Yu, J. & Ren, X. The role of miRNA-29 family in cancer. *Eur. J. Cell Biol.* **92**, 123–128 (2013).
131 Oak, S. R., Murray, L., Herath, A., Sleeman, M., Anderson, I., Joshi, A. D. *et al.* A micro RNA processing defect in rapidly progressing idiopathic pulmonary fibrosis. *PLoS ONE* **6**, e21253 (2011).
132 Fabbri, M., Garzon, R., Cimmino, A., Liu, Z., Zanesi, N., Callegari, E. *et al.* MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. *Proc. Natl Acad. Sci. USA* **104**, 15805–15810 (2007).
133 Yang, T., Liang, Y., Lin, Q., Liu, J., Luo, F., Li, X. *et al.* miR-29 mediates TGFbeta1-induced extracellular matrix synthesis through activation of PI3K-AKT pathway in human lung fibroblasts. *J. Cell Biochem.* **114**, 1336–1342 (2013).
134 Cushing, L., Kuang, P. & Lu, J. The role of miR-29 in pulmonary fibrosis. *Biochem. Cell Biol.* **93**, 109–118 (2015).
135 Mott, J. L., Kurita, S., Cazanave, S. C., Bronk, S. F., Werneburg, N. W. & Fernandez-Zapico, M. E. Transcriptional suppression of mir-29b-1/mir-29a promoter by c-Myc, hedgehog, and NF-kappaB. *J. Cell Biochem.* **110**, 1155–1164 (2010).
136 Wu, D. W., Hsu, N. Y., Wang, Y. C., Lee, M. C., Cheng, Y. W., Chen, C. Y. *et al.* c-Myc suppresses microRNA-29b to promote tumor aggressiveness and poor outcomes in non-small cell lung cancer by targeting FHIT. *Oncogene* **34**, 2072–2082 (2015).
137 Yoshino, H., Seki, N., Itesako, T., Chiyomaru, T., Nakagawa, M. & Enokida, H. Aberrant expression of microRNAs in bladder cancer. *Nat. Rev. Urol.* **10**, 396–404 (2013).
138 Fukumoto, I., Hanazawa, T., Kinoshita, T., Kikkawa, N., Koshizuka, K., Goto, Y. *et al.* MicroRNA expression signature of oral squamous cell carcinoma: functional role of microRNA-26a/b in the modulation of novel cancer pathways. *Br. J. Cancer* **112**, 891–900 (2015).
139 Kinoshita, T., Nohata, N., Hanazawa, T., Kikkawa, N., Yamamoto, N., Yoshino, H. *et al.* Tumour-suppressive microRNA-29s inhibit cancer cell migration and invasion by targeting laminin-integrin signalling in head and neck squamous cell carcinoma. *Br. J. Cancer* **109**, 2636–2645 (2013).
140 Matsuo, M., Nakada, C., Tsukamoto, Y., Noguchi, T., Uchida, T., Hijiya, N. *et al.* MiR-29c is downregulated in gastric carcinomas and regulates cell proliferation by targeting RCC2. *Mol. Cancer* **12**, 15 (2013).
141 Mizuno, K., Seki, N., Mataki, H., Matsushita, R., Kamikawaji, K., Kumamoto, T. *et al.* Tumor-suppressive microRNA-29 family inhibits cancer cell migration and invasion directly targeting LOXL2 in lung squamous cell carcinoma. *Int. J. Oncol.* **48**, 450–460 (2016).
142 Ouzounova, M., Vuong, T., Ancey, P. B., Ferrand, M., Durand, G., Le-Calvez Kelm, F. *et al.* MicroRNA miR-30 family regulates non-attachment growth of breast cancer cells. *BMC Genomics* **14**, 139 (2013).
143 Quintavalle, C., Donnarumma, E., Iaboni, M., Roscigno, G., Garofalo, M., Romano, G. *et al.* Effect of miR-21 and miR-30b/c on TRAIL-induced apoptosis in glioma cells. *Oncogene* **32**, 4001–4008 (2013).
144 Wu, T., Zhou, H., Hong, Y., Li, J., Jiang, X. & Huang, H. miR-30 family members negatively regulate osteoblast differentiation. *J. Biol. Chem.* **287**, 7503–7511 (2012).
145 Tsukasa, K., Ding, Q., Miyazaki, Y., Matsubara, S., Natsugoe, S. & Takao, S. miR-30 family promotes migratory and invasive abilities in CD133 pancreatic cancer stem-like cells. *Hum. Cell* **29**, 130–137 (2016).

146 Zhong, K., Chen, K., Han, L. & Li, B. MicroRNA-30b/c inhibits non-small cell lung cancer cell proliferation by targeting Rab18. *BMC Cancer* **14**, 703 (2014).
147 Yu, G., Herazo-Maya, J. D., Nukui, T., Romkes, M., Parwani, A., Juan-Guardela, B. M. *et al.* Matrix metalloproteinase-19 promotes metastatic behavior in vitro and is associated with increased mortality in non-small cell lung cancer. *Am. J. Respir. Crit. Care Med.* **190**, 780–790 (2014).
148 Konigshoff, M., Kramer, M., Balsara, N., Wilhelm, J., Amarie, O. V., Jahn, A. *et al.* WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. *J. Clin. Invest.* **119**, 772–787 (2009).
149 Berschneider, B., Ellwanger, D. C., Baarsma, H. A., Thiel, C., Shimbori, C., White, E. S. *et al.* miR-92a regulates TGF-beta1-induced WISP1 expression in pulmonary fibrosis. *Int. J. Biochem. Cell Biol.* **53**, 432–441 (2014).
150 Richeldi, L., du Bois, R. M., Raghu, G., Azuma, A., Brown, K. K., Costabel, U. *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **370**, 2071–2082 (2014).