Minireview
MicroRNA in lung cancer

P-Y Lin1,2, S-L Yu3,4,5 and P-C Yang*1,2,4,5
1Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan; 2Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan; 3Department of Clinical and Laboratory Sciences and Medical Biotechnology, National Taiwan University, Taipei, Taiwan; 4Division of Genomic Medicine, Research Center for Medical Excellence, National Taiwan University, Taipei, Taiwan

MicroRNAs (miRNAs) are small non-protein-coding RNAs that function as endogenous negative gene regulators. Dysfunctions of miRNAs are frequently found in malignancies, including lung cancer. In this review, we summarise the current understanding of miRNAs in lung cancer tumorigenesis, and highlight their potential in overcoming drug resistance, abetting histological sub-classification techniques, and serving as biomarkers for lung cancer risk stratification and outcome prediction.

Keywords: lung cancer; microRNA; oncogene; tumour suppressor; risk stratification; personalised medicine

Lung cancer is the leading cause of cancer mortality worldwide, and 80% of lung cancers are non-small cell lung cancers (NSCLCs) ( Jamal et al, 2009). Despite improvements in early diagnosis made possible by emerging technologies and newly developed chemo/targeted therapies that improve treatment responses, the overall 5-year survival for NSCLC patients remains low (15%) and the recurrence rate is high, even in early-stage groups ( Miller, 2005). The poor prognosis is due to late disease presentation, tumour heterogeneities within histological subtypes, and our relatively limited understanding of tumour biology. Emerging targeted therapies directed against specific cellular alterations require precise sub-classification of NSCLCs that is beyond the capabilities of standard histopathological diagnostic techniques. However, knowledge accumulated through genomic medicine creates the possibility of unravelling the remaining mysteries of lung cancer oncogenesis, and opens the door to molecular classification and risk stratification based on gene expression profiles and microRNA (miRNA) signatures.

MicroRNAs are small non-coding, endogenous, single-stranded RNAs that regulate gene expression (Bartel, 2004). Mature miRNAs and Argonaute (Ago) proteins form the RNA-induced silencing complex (RISC), which mediates post-transcriptional gene silencing through induction of messenger RNA (mRNA) degradation or translational inhibition ( Liu et al, 2004; Pillai et al, 2004). Target mRNA specification is determined by sequence complementarity between the seed sequence of an individual miRNA and the target mRNAs (Baek et al, 2008; Eulalio et al, 2008; Selbach et al, 2008; Bartel, 2009). Recent proteomic studies have revealed a broad spectrum of targets for each individual miRNA (Baek et al, 2008; Selbach et al, 2008). By regulating gene expression at the post-transcriptional level, miRNAs profoundly influence a wide variety of pathways, and their greatest impact is on developmental and oncogenic pathways ( Lee et al, 1993; Wightman et al, 1993; He et al, 2005, 2007; Johnson et al, 2005; Lu et al, 2005; Calin and Croce, 2006).

Half of all miRNA genes are found within or near chromosomal fragile sites, common breakpoints, or minimal regions of loss-of-heterozygositiy or amplification (Calin et al, 2004). Accumulating evidence shows that miRNAs are grossly dysregulated in human cancers, including NSCLC, and may serve as oncogenes or tumour suppressors (Croce, 2009). Recent studies have shown that not only can miRNAs be used to sub-classify NSCLCs (Bishop et al, 2010) but specific miRNA profiles may also predict prognosis and disease recurrence in early-stage NSCLCs (Yanaihara et al, 2006; Yu et al, 2008; Raponi et al, 2009; Seike et al, 2009; Patnaik et al, 2010). In this review, we briefly describe the biogenesis of miRNAs, their roles in lung cancer pathogenesis, and their potential use in NSCLC subgroup classification, risk stratification, and therapy. The stratification of lung cancer based on miRNA information is illustrated in Figure 1.

MICRONNA BIOGENESIS

MicroRNA genes are evolutionarily conserved and are located within the introns or exons of protein-coding genes, as well as in intergenic areas (Rodriguez et al, 2004). Canonically, miRNA genes are transcribed by RNA polymerase II or III into kilobase-long primary miRNA transcripts (pri-miRNAs). Pri-miRNAs are next cleaved into ∼70 nucleotide-long precursor miRNAs (pre-miRNAs) by the nuclear microprocessor complex formed by the RNome III Drosha and DiGeorge syndrome critical region gene 8 (DGCR8). The average human pre-miRNA contains a 33-base-pair hairpin stem, a terminal loop, and two single-stranded flanking regions upstream and downstream of the hairpin. Pre-miRNAs are next transported by the exportin-5/Ran GTPase complex into the cytoplasm, where miRNAs undergo maturation (Lee et al, 2003, 2004; Yi et al, 2003; Denli et al, 2004). In the cytoplasm, pre-miRNAs are cleaved by RNase III Dicer into an ∼22 nucleotide-long miRNA duplex and are unwound by helicase. The passenger strand is degraded, and the selected guide strand together with Ago protein activates RISC, resulting in mRNA degradation or translational inhibition, depending on the percentage of sequence complementarity between the miRNA 5′-seed and mRNA 3′-UTR element (Hammond et al, 2000; Diederichs and Haber, 2007).
DEFECTS IN THE MiRNA BIOGENESIS PATHWAY AND LUNG CANCER

Drosha, DGR8, and Dicer are the three best-established regulators of miRNA processing. Defects in the miRNA biogenesis machinery may be closely related to oncogenesis. Deletion of Dicer abrogates the production of mature miRNAs (Bernstein et al., 2003), and conditional deletion of Dicer1 enhances lung tumour development in a K-Ras-induced lung cancer mouse model (Kumar et al., 2007). In 2005, Karube et al. (2005) reported that reduced Dicer expression levels were correlated with poor survival in a cohort of 67 surgically resected NSCLC patients. This correlation has been confirmed in an ovarian cancer, three breast cancers, and a lung cancer cohort in which high Dicer and Drosha mRNA expression is associated with better overall and disease-free survival (Merritt et al., 2008).

MICRORNAs FUNCTION AS TUMOUR SUPPRESSORS OR ONCOGENES IN LUNG CANCER

Let-7 miRNAs as tumour suppressors

Let-7 was first identified in Caenorhabditis elegans as a regulator of the timing of cell fate determination (Reinhart et al., 2000). In C. elegans with mutant let-7, stem cells fail to exit the cell cycle and differentiate, but continue to divide, a hallmark of cancer cells (Reinhart et al., 2000). In humans, the let-7 family is a cluster of miRNAs whose genes map to different chromosomal regions that are frequently deleted in lung cancer (Calin et al., 2004). Cell studies have shown that let-7 miRNA overexpression in the A549 cell line inhibits cell growth and reduces cell-cycle progression (Johnson et al., 2007). In mouse NSCLC xenografts and orthotopic models, ectopic let-7g expression reduces tumour burden (Kumar et al., 2008), and intranasal let-7 administration represses lung adenocarcinoma (AD) formation (Esquela-Kerscher et al., 2008). Furthermore, reduced let-7 gene expression in NSCLC patients is correlated with poor prognosis (Takamizawa et al., 2004; Yanaihara et al., 2006), and a single nucleotide polymorphism in let-7 complementary site 6 of the K-RAS mRNA 3’-UTR is significantly associated with increased risk for NSCLC among moderate smokers (Chin et al., 2008). Collectively, these observations suggest a role for let-7 family miRNAs as tumour suppressors. In addition, let-7 miRNAs negatively regulate multiple oncogenes, including the RAS (Johnson et al., 2005), MYC (Kumar et al., 2007), and HMG2 (Lee and Dutta, 2007), and cell-cycle progression regulators, such as CDC25A, CDK6, and cyclin D2 (Johnson et al., 2007). Although a corresponding knockout mouse would be invaluable for in-depth studies of let-7 tumour suppressor functions, multiple copies of let-7 in the genome make generating such a model somewhat problematic (Calin et al., 2004).

ALL MEMBERS OF THE MiR-17-92 CLUSTER AND MiR-31 ARE ONCOGENES

All members of the miR-17-29 cluster (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92-1) are oncogenes that reside in 13q31.3 (He et al., 2005). These miRNAs cooperate with c-Myc to accelerate tumour development and help promote tumour neovascularisation (O’Donnell et al., 2005; Dews et al., 2006). The miR-17-92 cluster is overexpressed in small-cell lung cancer (Hayashita et al., 2005). Ebi et al. (2009) have confirmed this relationship and reported the association of miR-17-92 overexpression with RB inactivation. Their results suggest that this

Alternatively, pre-miRNAs are derived directly from size-matched introns. These so-called ‘mitrons’ skip the Drosha–DGR8 processing step and are spliced out of their host genes. These lariats are debranched, refolded into the stem-loop structure of typical pre-miRNAs, and then enter the canonical pathway (Okamura et al., 2007; Ruby et al., 2007).

A recent study by Suzuki et al. demonstrated that p53 interacts with the Drosha microprocessor complex through DEAD-box RNA helicase p68 (DDX5) and facilitates the processing of pri-miRNAs into pre-miRNAs. This study describes the p53-mediated post-transcriptional maturation of miRNAs, linking the core tumour suppressor p53 to the miRNA biogenesis pathway (Suzuki et al., 2009). These findings may provide an explanation for the widespread miRNA downregulation observed in human cancers, in which p53 is often dysfunctional (Lu et al., 2005).

In C. elegans with mutant let-7, stem cells fail to exit the cell cycle and differentiate, but continue to divide, a hallmark of cancer cells (Reinhart et al., 2000). In humans, the let-7 family is a cluster of miRNAs whose genes map to different chromosomal regions that are frequently deleted in lung cancer (Calin et al., 2004). Cell studies have shown that let-7 miRNA overexpression in the A549 cell line inhibits cell growth and reduces cell-cycle progression (Johnson et al., 2007). In mouse NSCLC xenografts and orthotopic models, ectopic let-7g expression reduces tumour burden (Kumar et al., 2008), and intranasal let-7 administration represses lung adenocarcinoma (AD) formation (Esquela-Kerscher et al., 2008). Furthermore, reduced let-7 gene expression in NSCLC patients is correlated with poor prognosis (Takamizawa et al., 2004; Yanaihara et al., 2006), and a single nucleotide polymorphism in let-7 complementary site 6 of the K-RAS mRNA 3’-UTR is significantly associated with increased risk for NSCLC among moderate smokers (Chin et al., 2008). Collectively, these observations suggest a role for let-7 family miRNAs as tumour suppressors. In addition, let-7 miRNAs negatively regulate multiple oncogenes, including the RAS (Johnson et al., 2005), MYC (Kumar et al., 2007), and HMG2 (Lee and Dutta, 2007), and cell-cycle progression regulators, such as CDC25A, CDK6, and cyclin D2 (Johnson et al., 2007). Although a corresponding knockout mouse would be invaluable for in-depth studies of let-7 tumour suppressor functions, multiple copies of let-7 in the genome make generating such a model somewhat problematic (Calin et al., 2004).
miR-31 is another example of an miRNA with oncogenic properties (termed an oncomir) in lung cancer. As reported by Liu et al., knockdown of miR-31 represses lung cancer cell clonal growth and in vivo tumourigenicity. Their data show that miR-31 functions as an oncomir by directly repressing the tumour suppressors LAT52 and PPP2R2A (Liu et al., 2010). This miR-31/LAT52/PPP2R2A pathway constitutes a new growth regulator in lung cancer.

MICRONAS AND CONVENTIONAL CHEMOTHERAPY FOR NSCLCs

The selection for chemotherapy-resistant cells is often observed in platinum-based chemotherapy, currently the main regimen in NSCLC treatment (Seve and Dumontet, 2005), and is a key cause of chemotherapeutic failure. A recent in vitro study by Galluzzi et al. (2010) showed that miR-630 inhibits p53-regulated pro-apoptotic signalling pathways that are specifically induced by cisplatin and carboplatin. This is one example demonstrating that the role of miRNAs may involve chemosensitivity/resistance determination and suggesting the possibility that manipulating miRNAs may be potentially useful to modulate the cancer chemoresistance.

MICRONAS AND TARGETED THERAPIES

Epidermal growth factor receptor (EGFR) signalling and EGFR mutations have been a major focus of lung cancer studies conducted during the past 5 years. Epidermal growth factor receptor is one of the most common proto-oncogenes in lung cancer. Leucine-to-arginine substitution at position 858 (L858R) and deletion mutants in exon 19 constitute 90% of lung cancer-specific EGFR-activating mutations. These mutations induce lung AD in a mouse model and confer hypersensitivity to EGFR–tyrosine kinase inhibitors (EGFR–TKIs) in humans (Rosell et al., 2009).

Several recent studies have uncovered a relationship between the EGFR signalling pathway and miRNAs. Weiss et al. (2008) showed that miR-126 is a direct regulator of EGFR. miR-126b loss-of-heterozygosity is frequently found in NSCLC patients and is positively correlated with clinical response and survival after gefitinib treatment. In addition, Cho et al. (2009) showed that restoration of the tumour suppressor miR-145 inhibits cancer cell growth in lung AD patients with EGFR-activating mutations. Furthermore, miR-7, an miRNA frequently downregulated in lung cancer, has been shown to suppress EGF and Raf1 mRNA expression. It also attenuates the activation of Akt and ERK, two key players in the EGFR signalling pathway, suggesting that miR-7 negatively regulates the EGFR pathway (Webster et al., 2009). Finally, miR-21 is upregulated under conditions in which EGFR signalling is activated, especially in the context of EGFR-activating mutations, and is suggested to be related to lung carcinogenesis in never smokers (Seike et al., 2009). Growing evidence from miRNA studies may help clarify the role of the EGFR network in lung cancer oncogenesis and provide a clue to solve EGFR–TKI resistance problems.

The Apo2L/tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), is a member of the TNF family known to induce apoptosis in a variety of cancers (Schafer et al., 2007). Treatment with TRAIL induces programmed cell death in cancer cells. However, a significant proportion of cancers are resistant to TRAIL-induced apoptosis through different mechanisms. Garofalo et al. (2009) showed that miR-27 and miR-222 contribute to lung cancer resistance to TRAIL therapy by downregulating PTEN and TIMP3 tumour suppressors. These observations hint at the extent to which a greater knowledge of miRNAs might bring a deeper understanding of drug-resistance mechanisms, and suggest a future role for miRNAs as a solution to the drug resistance problem.

MICRONAS IN NSCLC HISTOLOGICAL DIFFERENTIATION, RISK STRATIFICATION, AND OUTCOME PREDICTION

Histological differentiation

With the emergence of targeted therapies directed against specific molecular events or entities, accurate classification of tumours into AD and squamous cell carcinoma (SCC) becomes a necessity. However, this can be challenging, especially in cases in which biopsy/aspirate specimens are small or tumours are poorly differentiated. miR-205 is reported to be a useful marker for differentiating SCC from non-SCC NSCLCs, with a sensitivity of 96% and specificity of 90%, even in small biopsies from poorly differentiated tumours (Lebanony et al., 2009; Bishop et al., 2010). Landi et al. (2010) also reported a five-miRNA signature (miR-25, miR-34c-5p, miR-191, let-7e, and miR-34a) that accurately differentiated SCC from AD, and the lower expression level of this signature correlated with poor overall survival among SCC patients. This is a further step beyond the traditional protein markers used in immunohistochemical diagnosis of equivocal cases. It is anticipated that miRNA markers will ultimately also be found for AD.

Risk stratification and outcome prediction

Risk stratification and prognosis assessment have become a major concern in the era of personalised medicine. Gene expression profiling has reached a plateau in this regard (Garber et al., 2001; Shedden et al., 2008), although recent miRNA studies show great promise (Yanaihara et al., 2006; Yu et al., 2008; Raponi et al., 2009).

Yanaihara et al. (2006) reported that high miR-155 and low miR-let7a-2 expression correlated with poor overall survival in lung AD patients. Our group also identified a five-miRNA signature (miR-137, miR-372, miR-182*, miR-221, and let-7a) that correlated with disease-free survival in a cohort of 122 NSCLC patients (Yu et al., 2008). In addition, Raponi et al. reported that miR-146b is a robust predictor of overall survival in SCC. High miR-146b expression correlated with a poor overall survival in SCC patients and the same trend was also observed in the expression level of miR-155 among the same group of patients (Raponi et al., 2009). The pathway prediction of miR-146b-targeted genes revealed a significant overlap of biological pathways in their previously reported 50-gene expression signature (Beer et al., 2002; Raponi et al., 2009). Patnaik et al. (2010) also defined an miRNA signature that predicted post-operative recurrence of stage I NSCLCs. It is clearly evident from these studies that, as is the case with gene expression profiling, miRNA signatures suggested by different groups are almost non-overlapping. This could be because of the different experimental platforms used (qRT–PCR versus different groups or entities), batch effects inherent in the microarray expression profiling, miRNA signatures suggested by different pathways in their previously reported systematic studies are needed to clarify these issues. In addition, new modalities, such as next-generation sequencing, may provide tools to enhance the prospects of miRNA research.

A recent study by Hu et al. (2010) reported a four-miRNA signature (miR-486, miR-30d, miR-1, and miR-499) that predicted survival of stage I to IIIa NSCLCs. Unlike all previous studies, their miRNAs were identified in serum using a Solexa platform (Nanjing Medical University, Nanjing University and Jiangsu Cancer Hospital, Nanjing, China). Although this represents a relative non-invasive approach, questions remain as to the representativeness of serum miRNA profiles in solid cancers, given that this approach fails to identify miRNAs commonly found in lung cancer tissues.
PERSPECTIVES
Numerous miRNAs are dysregulated in cancers, and a single miRNA can have multiple targets involved in different oncogenic pathways. Accumulating evidence also suggests a role for miRNAs in fighting drug resistance. These properties make miRNAs attractive targets in cancer therapy. However, the fact that one miRNA may target hundreds of mRNAs deserves special consideration, insofar as it implies the possibility of unpredictable side effects, even if a specific miRNA is effectively targeted. A greater understanding of miRNA biology and the development of suitable delivery systems are required to translate these basic research results into clinical practice. In addition, miRNAs may abet the histological characterisation of NSCLC differentiation, especially in cases in which biopsy/aspiration specimens are inadequate or tumours are poorly differentiated. This is especially important when targeted therapy is the treatment of choice. Risk stratification and drug-response prediction are the central elements of personalised medicine. During recent years, research has focused mainly on gene expression profiling and a number of important studies have been published. As gene expression profiling reaches a plateau and begins to face limitations, miRNA profiling returns to the stage of clinical significance.

REFERENCES

Baek D, Villen J, Shin C, Camargo FD, Gygi SP, Bartel DP (2008) The impact of microRNAs on protein output. Nature 455: 64 – 71

Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116: 281 – 297

Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. Cell 136: 215 – 233

Beer DG, Kardia SL, Huang CC, Giordano TJ, Levin AM, Misek DE, Lin L, Chen G, Ghosh S, Thomas DG, Li J, Sudderth D, Lange C, Christiani DC, Bova GS, Tsimelzon A, Torok-Storb B, Wang Q, Aizer RA, Safferman AS, Berchuck A, Kris MG, Blot WJ, Hanis C, Moore RH, Sternberg CN, Hamilton SR,testing. J Clin Oncol 28: 9628 – 9632

Elliott AL, Huntzinger E, Izaurralde E (2008) Getting to the root of miRNA-mediated gene silencing. Cell 132: 9 – 14

Galluzzi L, Morsseli E, Vitale I, Kepp O, Senovilla L, Criollo A, Servant N, Paccard C, Hupé P, Robert T, Ripoche H, Lazar V, Harel-Bellan A, Dessen P, Barillot E, Kroemer G (2010) miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res 70: 1793 – 1803

Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Lin JD, Cohen SR, Sander C, Muthuswamy SK, Chang HC, Brown PO, Botstein D, Petersen I (2005) Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA 102: 13784 – 13789

Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, Taccioli C, Pichiorri F, Alder H, Secchiero P, Gasparini P, Gonelli A, Costinean S, Acunzo M, Bedognetti E, Croce CM (2009) miR-21 regulates PTEN and TIMP3 expression and mediates drug resistance. Nat Cell Biol 11: 592 – 602

He L, He X, Lim LP, Hannon GJ (2007) A microRNA component of the p53 tumour suppressor network. Nature 447: 1130 – 1136

Hickson IOD, Chapman RA, Sughra M, Quail SC, Morris DS, Conigliaro T, Vos J, Schechter P, Gambacorti-Passerini C, Miller VA, Seitz C, Lehmann CD, Sorensen CO, Herawi M, Ellis IO, Kallioniemi OP, Meijers-Heijboer H, Camidge DR, Morroni C, Seitz H, Fens K, Perus F, CFantastic

Hosono Y, Yatabe Y, Matsuyama Y, Yamaguchi T, Osaka H, Suzuki M, Takahashi T (2009) Counterbalance between RB inactivation and mir-17-92 overexpression in reactive oxygen species and DNA damage induction in lung cancers. Oncogene 28: 3371 – 3379

Huang CC, Thomas DG, Li J, Sudderth D, Lange C, Christiani DC, Bova GS, Tsimelzon A, Torok-Storb B, Wang Q, Aizer RA, Safferman AS, Berchuck A, Kris MG, Blot WJ, Hanis C, Moore RH, Sternberg CN, Hamilton SR,testing. J Clin Oncol 28: 9628 – 9632

Elliott AL, Huntzinger E, Izaurralde E (2008) Getting to the root of miRNA-mediated gene silencing. Cell 132: 9 – 14

Galluzzi L, Morsseli E, Vitale I, Kepp O, Senovilla L, Criollo A, Servant N, Paccard C, Hupé P, Robert T, Ripoche H, Lazar V, Harel-Bellan A, Dessen P, Barillot E, Kroemer G (2010) miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res 70: 1793 – 1803

Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Lin JD, Cohen SR, Sander C, Muthuswamy SK, Chang HC, Brown PO, Botstein D, Petersen I (2005) Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA 102: 13784 – 13789

Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, Taccioli C, Pichiorri F, Alder H, Secchiero P, Gasparini P, Gonelli A, Costinean S, Acunzo M, Bedognetti E, Croce CM (2009) miR-21 regulates PTEN and TIMP3 expression and mediates drug resistance. Nat Cell Biol 11: 592 – 602

He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Hammond SJ, Bernstein E, Beach D, Hannon GJ (2000) An RNA-directed DNA nuclease mediates post-transcriptional gene silencing in Drosophila cells. Nature 404: 293 – 329

Hayashiya T, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, Yatabe Y, Kawahara K, Sekido Y, Takahashi T (2005) A polycistronic microRNA cluster, miR-17-92, is overexpressed in reactive oxygen species and DNA damage induction in lung cancers. Oncogene 24: 3371 – 3379

Huang CC, Thomas DG, Li J, Sudderth D, Lange C, Christiani DC, Bova GS, Tsimelzon A, Torok-Storb B, Wang Q, Aizer RA, Safferman AS, Berchuck A, Kris MG, Blot WJ, Hanis C, Moore RH, Sternberg CN, Hamilton SR,testing. J Clin Oncol 28: 9628 – 9632

Elliott AL, Huntzinger E, Izaurralde E (2008) Getting to the root of miRNA-mediated gene silencing. Cell 132: 9 – 14

Galluzzi L, Morsseli E, Vitale I, Kepp O, Senovilla L, Criollo A, Servant N, Paccard C, Hupé P, Robert T, Ripoche H, Lazar V, Harel-Bellan A, Dessen P, Barillot E, Kroemer G (2010) miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res 70: 1793 – 1803

Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Lin JD, Cohen SR, Sander C, Muthuswamy SK, Chang HC, Brown PO, Botstein D, Petersen I (2005) Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA 102: 13784 – 13789

Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, Taccioli C, Pichiorri F, Alder H, Secchiero P, Gasparini P, Gonelli A, Costinean S, Acunzo M, Bedognetti E, Croce CM (2009) miR-21 regulates PTEN and TIMP3 expression and mediates drug resistance. Nat Cell Biol 11: 592 – 602

He L, Thomson JM, Hemmann MT, Hernando-Monge E, Mu D, Goodson S, Powers S, Carden-Cardo C, Lowe SW, Hannon GJ, Hammond SM (2005) A microRNA polycistron as a potential human oncogene. Nature 435: 828 – 833

He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, Jackson AL, Linsley PS, Chen C, Lowe SW, Cleary MA, Hannon GJ (2007) A microRNA component of the p53 tumour suppressor network. Nature 447: 1130 – 1136

Hu Z, Chen X, Zhao Y, Tian T, Lin G, Shu Y, Chen Y, Xu L, Zen K, Zhang C, Shen H (2010) Serum microRNA signatures identified in a genome-wide serum microRNA expression profiling predict survival of non-small-cell lung cancer. J Clin Oncol 28: 1721 – 1726

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59: 223 – 249

© 2010 Cancer Research UK

MicroRNAin lung cancer
P.Y Lin et al

signature is a rising star that may provide new resolutions to old problems. It is difficult to say whether miRNA signature is superior or inferior to gene expression profiling, with respect to risk stratification and outcome prediction. What is clear, however, is that the more we understand cancer biology, the more likely we are to translate these laboratory-oriented studies into clinical practice. Finally, miRNAs are much more stable in serum and plasma than in miRNAs, raising the exciting prospect that miRNAs might be used as non-invasive biomarkers for disease monitoring and histological classification under specific circumstances. Going forward, insights gained from miRNA studies may open a new era in lung cancer treatments, providing improved patient selection for targeted agents, and forming the basis for the development of novel therapeutics and/or early disease biomarkers.

ACKNOWLEDGEMENTS

This work is supported by NRPGM (NSC98-3112-B-002-041) and NTU 97R0066-08.
Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labouriere E, Reintzel KL, Brown D, Slack F (2005) RAS is regulated by the let-7 microRNA family. Cell 120: 635–647

Johnson CD, Esquela-Kersch A, Stefani G, Byrom M, Kelnar K, Ovcharenko D, Wilson M, Wang X, Shelton J, Shingara J, Chin L, Brown D, Slack FJ (2007) The let-7 microRNA represses cell proliferation pathways in human cells. Cancer Res 67: 7713–7722

Karube Y, Tanaka H, Osada H, Tomida S, Tatamatsu Y, Yanagisawa K, Yatabe Y, Takamizawa J, Miyoshi S, Mitsudomi T, Takahashi T (2005) Reduced expression of Dicer associated with poor prognosis in lung cancer patients. Cancer Sci 96: 111–115

Kumar MS, Lu J, Mercer KL, Golub TR, Jacks T (2007) Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet 39: 673–677

Kumar MS, Erkeland SJ, Pester RE, Chen CY, Ebert MS, Sharp PA, Jacks T (2008) Suppression of non-small cell lung tumor development by the let-7 microRNA family. Proc Natl Acad Sci USA 105: 3903–3908

Landi MT, Zhao Y, Rotunno M, Koshiol J, Liu H, Bergen AW, Rubagotti M, Goldstein AM,4 Linnoila I, Marincola FM, Tucker MA, Bertazzi PA, Pesatori AC, Caporaso NE, MShane LM, Wang E (2010) MicroRNA expression differentiates histology and predicts survival of lung cancer. Clin Cancer Res 16: 430–441

Lee YS, Dutta A (2007) The tumor suppressor microRNA-let7 represses the HMGA2 oncogene. Genes Dev 21: 1025–1030

Lee YC, Chen HS, Su TJ, Chiang CC, Li HN, Hong QS, Su HY, Chen CC, Ying PY, Lin PY et al (2008) Suppression of non-small cell lung tumor development by the let-7 microRNA family. Proc Natl Acad Sci USA 105: 3903–3908

Laboury D, Benjamin H, Gilad S, Ezagouri M, Dov A, Ashkenazi K, Landi MT, Zhao Y, Rotunno M, Koshiol J, Liu H, Bergen AW, Rubagotti M, Goldstein AM,4 Linnoila I, Marincola FM, Tucker MA, Bertazzi PA, Pesatori AC, Caporaso NE, MShane LM, Wang E (2010) MicroRNA expression differentiates histology and predicts survival of lung cancer. Clin Cancer Res 16: 430–441

Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Radmark O, Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN (2004) MicroRNA expression profiling of human lung adenocarcinomas. Cancer Res 64: 3646–3654

Lee Y, Chen HY, Chang GC, Chen CY, Chen HW, Singh S, Cheng CL, Yu CJ, Lee YC, Chen HS, Su TJ, Chiang CC, Li HN, Hong QS, Su HY, Chen GC, Chen WJ, Liu CC, Chan WK, Chen WJ, Li KC, Chen JJ, Yang PC (2008) MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell 14: 48–57