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Role of microRNAs in the metastasis of non-small cell lung cancer

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1. ABSTRACT

Lung cancer is the leading cause of cancer death. Non-small cell lung cancer (NSCLC), including the squamous cell carcinoma, large cell carcinoma and adenocarcinoma subtypes, accounts for more than 80% of primary lung cancer cases. Understanding the mechanisms underlying NSCLC metastasis is essential for the improvement of anticancer therapies. Recent studies have shown that microRNAs (miRNAs) play very important roles in the progression of NSCLC from its initial stages to metastasis. This review discusses these central roles of miRNAs in the NSCLC metastasis.

2. INTRODUCTION

Lung cancer is one of the leading causes of cancer death worldwide, with an overall five-year survival rate of only 11% (1, 2). Non-small cell lung cancers (NSCLC) account for more than 80% of primary lung cancer cases. Three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma (3). Cancer metastases are the main cause of death of NSCLC patients, and they are currently a hot topic in the lung cancer research. Despite recent advances in understanding lung cancer metastasis, the prognosis for these patients is still unfavorable. The median survival time of patients with untreated metastatic NSCLC is only four to five months, with one-year survival rate of only 10% (4). Thus, it is essential to further increase our understanding of the mechanisms underlying NSCLC metastasis is in order to improve the treatment of this disease.

MicroRNAs (miRNA) are small non-coding RNA molecules, of about 22 nucleotides, which target mRNAs through base pairing in 3'-untranslated region of mRNA. miRNA recognition leads to the cleavage or translational repression of target mRNA (5,6). This process plays a crucial role in the transcriptional and post-transcriptional regulation of gene expression (7). A previous lung cancer study, investigating a panel of signature miRNAs, including metastatic biomarkers, showed significant changes in their levels (8). These results suggest that miRNA may be involved in the lung cancer metastasis, including NSCLC metastasis.

3. MICRORNAs IN THE INVASION AND MIGRATION OF NON-SMALL CELL LUNG CANCER CELLS

Cell invasion and migration are fundamental steps in NSCLC metastasis. Cancer cells acquire migratory and invasive capacities during transformation. Thus, we review first miRNA roles in the invasion and migration of cancer cells at the early stages of NSCLC metastasis.

3.1. MicroRNAs in the non-small cell lung cancer invasion

miRNAs were demonstrated to both promote and suppress NSCLC cell invasion. For example, miR-10b overexpression promotes NSCLC cell invasion (12). Interestingly, miR-196a stimulates tumor cell invasion

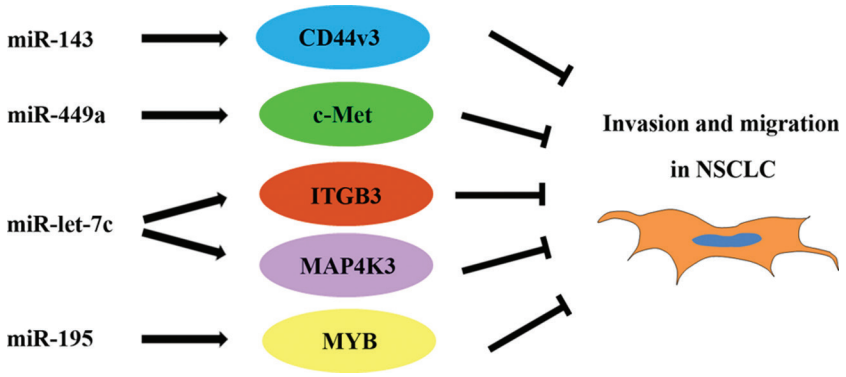

Figure 1. MicroRNAs (miRNAs) inhibits invasion and migration in human non-small cell lung cancer (NSCLC) by targeting several genes. MiR-143 inhibits invasion and migration of human NSCLC by targeting CD44v3, miR-449a by targeting c-Met, miR-let-7c by targeting ITGB3 and MAP4K3 and miR-195 by targeting MYB.

through targeting of *HOXA5* gene, which is a regulator of lung development (13), while miR-133b regulates the invasion through epidermal growth factor receptor signaling pathway (9). MiR-21 enhances NSCLC invasion through downregulation of the tumor suppressor PTEN (14), and this simultaneously promotes migration (15). MiR-212 enhances the invasion and migration of NSCLC cells (16). Furthermore, the miR-106b-25 cluster enhances the invasion and migration of H1299 NSCLC cells through the direct inhibition of *beta-TRCP2* gene. TRCP protein is involved in the Wnt signaling pathway, and its activation leads to the upregulation of Snail expression (17). These studies show that miRNAs are able to act on both invasion and migration of NSCLC cells.

However, previous investigations also described another type of miRNAs, such as miR-22, miR-34b, miR-203, and miR-128, which can inhibit NSCLC cell invasion (18-20). For example, the methylation of miR-34b is associated with regulation of lymphatic invasion (10). It inhibits the invasion of lung cancer cells through the interaction with metastasis-associated gene 1 (MTA1), which is involved in the carcinogenesis and metastasis. Several different studies demonstrated that miR-101 inhibits NSCLC invasion in both human tissues and cell lines (21). Further studies of lung cancer cell lines identified several targets, such as zeste homolog 2 (EZH2) and polycomb repressive complex 2 (PRC2), as responsible for this tumor suppression (22). In another study, miRNA let-7a was shown to inhibit the invasion of NSCLC cell line 95D, by targeting the translation of K-RAS and HMGA2 (23). Furthermore, experiments showed that miR-30c controls NSCLC cell invasion by targeting MTA1 (24).

In summary, miRNAs play a dual role in regulating NSCLC cell invasion through different targets, suggesting their complex role in tumor regulation. Understanding the mechanisms of miRNA modulation of NSCLC invasion may provide novel approaches in the development of metastatic NSCLC therapies, aimed at early stages of metastasis.

3.2. MicroRNAs in the migration of non-small cell lung cancer cells

In vitro studies and in-depth bioinformatic analyses have found that several lung cancer-related miRNAs, such as miR-7 and miR-ephrin-A1-LNP complex, can negatively regulate tumor migration signaling pathways (25-27). Furthermore, studies on five NSCLC cell lines (H358, H1650, H1975, HCC827, and H292) and human NSCLC tissues show that miR-146a inhibits tumor cell migration and distant metastasis in NSCLC (28). Park and colleagues showed that MiR-let-7 inhibits A549 cell migration (29).

Moreover, studies showed that miR-183 simultaneously inhibits the migration and invasion of lung cancer cells by targeting the VIL2-coding-protein Ezrin (30). MiR-193b suppresses the migration and invasion capacities of A549 NSCLC cell line (31). These results suggest that miRNAs can inhibit both migration and invasion of lung cancer cells.

miRNAs participate in the suppression of migration and invasion of cancer cells via different targets. For instance, miR-143 inhibits the invasion and migration of human NSCLC cells by targeting CD44v3 (32), miR-449a by targeting c-Met (33), miR-let-7c by targeting ITGB3 and MAP4K3 (34), and miR-195 by targeting MYB (35) (Figure 1). The miRNA efficiency in controlling the migration and invasion of lung cancer cells can be altered by AMO (anti-miRNA oligonucleotide)-CLOSs (cationic lipid binding oligonucleotide (AMO)-loaded SLNs) (36). Taken together, these results demonstrate that miRNAs undoubtedly play significant roles in the regulation of both invasion and migration in metastatic NSCLC.

4. MICRORNAs IN THE NON-SMALL CELL LUNG CANCER METASTASIS

In A549 NSCLC cells, epithelial-mesenchymal transition leads to upregulation of 18 and downregulation

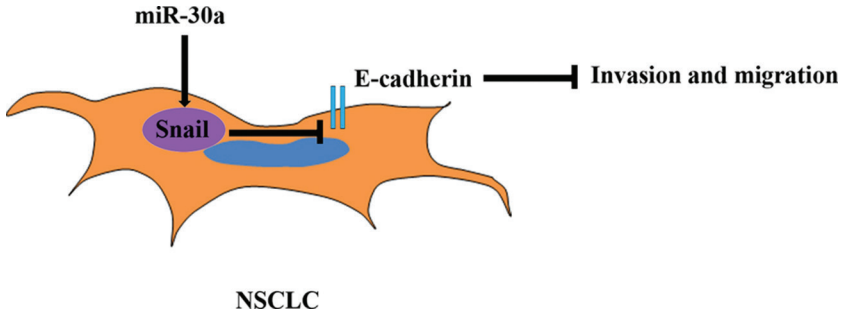

Figure 2. MicroRNA (miRNA)-30a inhibits metastasis in non-small cell lung cancer (NSCLC). MiR-30a induces Snail downregulation and E-cadherin upregulation, which leads to the inhibition of invasion and metastasis of NSCLC.

of 33 different miRNAs (37), suggesting that miRNAs may be involved in the regulation of NSCLC metastasis.

4.1. Pro-metastatic effects of miRNAs

Several miRNAs have been involved in the promotion of lung cancer metastasis. MiR-135b enhances the invasive and migratory properties of cancer cells *in vitro* and promotes cancer metastasis *in vivo* through interactions with multiple targets in the Hippo pathway (38). Furthermore, miR-7 promotes lung cancer metastasis, and another miRNA, miR-378, is associated with brain metastasis in NSCLC (39), and it targets protein kinase C alpha (PKC-α) (40).

The number of lymph node metastases can predict the survival of NSCLC patients, even those who have undergone lung resection (41), and this makes this number a significant indicator of the severity of NSCLC. Some miRNAs are also involved in lymph node metastasis. The increased expression levels of several miRNAs (including miR-10b, miR-451, miR-155, miR-19b, miR-9, miR-210, miR-21, and miR-1258) are correlated with the presence of regional lymph node metastases in NSCLC patients (42-49). Among these miRNAs, miR-21 is an independent positive prognostic factor in NSCLC patients with lymph node metastases (48), while miR-1258 targets heparanase expression and may influence NSCLC metastasis (49). The decreased expression of miRNAs (including miR-146a, miR-100, miR-375, miR-148a, miR-200, and miR-181b) is also closely related to lymph node metastases in NSCLC patients (45, 61-65). However, the targets and mechanisms underlying these miRNA effects are still unclear.

4.2. Anti-metastatic effects of miRNAs

In addition to promoting metastasis in NSCLC, several miRNAs, such as miR-125a-5p, can also inhibit it (50). miRNAs inhibit lung cancer metastasis through several different targets. For instance, overexpression of miR-7 can suppress the metastatic potential of lung cancer cells *in vitro* and *in vivo* by targeting phosphoinositide-3-kinase, the regulatory subunit of the 3 (PIK3R3)/Akt pathway (51). Furthermore, miR-182 inhibits metastasis by targeting FOXO3 (52) and miR-33a is involved in suppression of lung cancer bone metastasis (53). MiR-200c (54) as well as miR-503 (55) can suppress cell invasion *in vitro* and metastasis formation *in vivo* when they are reintroduced into NSCLC cells. Further studies on the mechanisms of metastatic NSCLC reveal that miR-30a can suppress metastasis by targeting Snail (56) (Figure 2). Snail is one of the most potent transcriptional suppressors of E-cadherin (57), and suppression of Snail in different animal models leads to increased expression of E-cadherin and suppression of tumorigenesis and EMT (58, 59). Metastatic NSCLC is also inhibited by miRNA-193a-3p through downregulation of the activity of the ERBB4/PIK3R3/mTOR/S6K2 signaling pathway (60).

5. CONCLUSIONS

In conclusion, miRNAs are involved in all stages of NSCLC progression, from cell invasion, migration, to eventual tumor metastasis. Furthermore, miRNAs regulate NSCLC metastasis in two distinct ways, as promoters or suppressors of metastasis, through targeting of different genes. Taking into consideration these complex functions of miRNAs, intensive research on the roles of miRNAs in NSCLC metastasis, which will provide new potential targets for the development of therapies for NSCLC, and improving the patient survival, is urgently needed.

6. ACKNOWLEDGEMENTS

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7. REFERENCES

1. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012.*CA Cancer J Clin* 62:10-29 (2012)

DOI: 10.3322/caac.20138

2. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I: Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. *Lancet Oncol* 13(9):784–796 (2007)
DOI: 10.1016/S1470-2045(07)70246-2

3. Bi N, Yang M, Zhang L, Chen X, Ji W, Ou G, Lin D, Wang L: Cyclooxygenase-2 genetic variants are associated with survival in unresectable locally advanced non-small cell lung cancer. *Clin Canc Res* 32:2383–2390 (2010)
DOI: 10.1158/1078-0432.CCR-09-2793

4. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, Hodson DI, Clark DA, Feld R, Arnold AM, *et al*: Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer--report of a Canadian multicenter randomized trial. J Clin Oncol 6(4):633-41 (1988)
No doi was found.

5. Farazi TA, Spitzer JI, Morozov P, Tuschl T: miRNAs in human cancer. *J Pathol* 223(2):102–115 (2011)
DOI: 10.1002/path.2806

6. Bartel DP: MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116(2):281–297 (2004)
DOI: 10.1016/S0092-8674(04)00045-5

7. Chen K, Rajewsky N: The evolution of gene regulation by transcription factors and microRNAs. *Nat Rev Genet* 8(2):93-103 (2007)
DOI: 10.1038/nrg1990

8. Liu H, Park J, Manning C, Goehlmann HW, Marshall DJ: Metastatic signature in lung cancer is associated with sensitivity to anti-integrin αV monoclonal antibody intetumumab. *Genes Chromosomes Cancer* 53(4):349-57 (2014)
DOI: 10.1002/gcc.22145

9. Liu L, Shao X, Gao W, Zhang Z, Liu P, Wang R, Huang P, Yin Y, Shu Y: MicroRNA-133b inhibits the growth of non-small-cell lung cancer by targeting the epidermal growth factor receptor. *FEBS J* 279(20):3800-12 (2012)
DOI: 10.1111/j.1742-4658.2012.08741.x

10. Watanabe K, Emoto N, Hamano E, Sunohara M, Kawakami M, Kage H, Kitano K, Nakajima J, Goto A, Fukayama M, Nagase T, Yatomi Y, Ohishi N, Takai D: Genome structure-based screening identified epigenetically silenced microRNA associated with invasiveness in non-small-cell lung cancer. *Int J Cancer* 130(11):2580-90 (2012)
DOI: 10.1002/ijc.26254

11. Zhu X, Zhang X, Wang H, Song Q, Zhang G, Yang L, Geng J, Li X, Yuan Y, Chen L: MTA1 gene silencing inhibits invasion and alters the microRNA expression profile of human lung cancer cells. *Oncol Rep* 28(1):218-24 (2012)
No doi was found.

12. Liu Y, Li M, Zhang G, Pang Z: MicroRNA-10b overexpression promotes non-small cell lung cancer cell proliferation and invasion. *Eur J Med Res* 18:41 (2013)
DOI: 10.1186/2047-783X-18-41

13. Liu XH, Lu KH, Wang KM, Sun M, Zhang EB, Yang JS, Yin DD, Liu ZL, Zhou J, Liu ZJ, De W, Wang ZX: MicroRNA-196a promotes non-small cell lung cancer cell proliferation and invasion through targeting HOXA5. *BMC Cancer* 12:348 (2012)
DOI: 10.1186/1471-2407-12-348

14. Zhang JG, Wang JJ, Zhao F, Liu Q, Jiang K, Yang GH: MicroRNA-21 (miR-21) represses tumor suppressor PTEN and promotes growth and invasion in non-small cell lung cancer (NSCLC) *Clin Chim Acta* 411(11-12):846-52 (2010)
DOI: 10.1016/j.cca.2010.02.074

15. Liu ZL, Wang H, Liu J, Wang ZX: MicroRNA-21 (miR-21) expression promotes growth, metastasis, and chemo- or radioresistance in non-small cell lung cancer cells by targeting PTEN. *Mol Cell Biochem* 372(1-2):35-45 (2013)
DOI: 10.1007/s11010-012-1443-3

16. Li Y, Zhang D, Chen C, Ruan Z, Li Y, Huang Y: MicroRNA-212 displays tumor-promoting properties in non-small cell lung cancer cells and targets the hedgehog pathway receptor PTCH1. *Mol Biol Cell* 23(8):1423-34 (2012)
DOI: 10.1091/mbc.E11-09-0777

17. Savita U, Karunagaran D: MicroRNA-106b-25 cluster targets β-TRCP2, increases the expression of Snail and enhances cell migration and invasion in H1299 (non small cell lung cancer) cells. *Biochem Biophys Res Commun* 434(4):841-7 (2013)
DOI: 10.1016/j.bbrc.2013.04.025

18. Ling B, Wang GX, Long G, Qiu JH, Hu ZL: Tumor suppressor miR-22 suppresses lung cancer cell progression through post-transcriptional regulation of ErbB3. *J Cancer Res Clin Oncol* 138(8):1355-61 (2012)
DOI: 10.1007/s00432-012-1194-2

19. Jin J, Deng J, Wang F, Xia X, Qiu T, Lu W, Li X, Zhang H, Gu X, Liu Y, Cao W, Shao W: The expression and function of microRNA-203 in lung cancer. *Tumour Biol* 34(1):349-57 (2013)
DOI: 10.1007/s13277-012-0556-3

20. Wu DW, Cheng YW, Wang J, Chen CY, Lee H: Paxillin predicts survival and relapse in non-small cell lung cancer by microRNA-218 targeting. *Cancer Res* 70(24):10392-401 (2010)
DOI: 10.1158/0008-5472.CAN-10-2341

21. Zhang JG, Guo JF, Liu DL, Liu Q, Wang JJ: MicroRNA-101 exerts tumor-suppressive functions in non-small cell lung cancer through directly targeting enhancer of zeste homolog 2. *J Thorac Oncol* 6(4):671-8 (2011)
DOI: 10.1097/JTO.0b013e318208eb35

22. Cho HM, Jeon HS, Lee SY, Jeong KJ, Park SY, Lee HY, Lee JU, Kim JH, Kwon SJ, Choi E, Na MJ, Kang J, Son JW: microRNA-101 inhibits lung cancer invasion through the regulation of enhancer of zeste homolog 2. *Exp Ther Med* 2(5):963-967 (2011)
No doi was found.

23. Wang YY, Ren T, Cai YY, He XY: MicroRNA let-7a inhibits the proliferation and invasion of nonsmall cell lung cancer cell line 95D by regulating K-Ras and HMGA2 gene expression. *Cancer Biother Radiopharm* 28(2):131-7 (2013)
DOI: 10.1089/cbr.2012.1307

24. Xia Y, Chen Q, Zhong Z, Xu C, Wu C, Liu B, Chen Y: Down-regulation of miR-30c promotes the invasion of non-small cell lung cancer by targeting MTA1. *Cell Physiol Biochem* 32(2):476-85 (2013)
DOI: 10.1159/000354452

25. Zhang H, Yang H, Zhang R, Zhang C, Zhang J, Li D: In-depth bioinformatic analysis of lung cancer-associated microRNA targets. *Oncol Rep* 30(6):2945-56 (2013)
No doi was found.

26. Xiong S, Zheng Y, Jiang P, Liu R, Liu X, Chu Y: MicroRNA-7 inhibits the growth of human non-small cell lung cancer A549 cells through targeting BCL-2. *Int J Biol Sci* 7(6):805-14 (2011)
DOI: 10.7150/ijbs.7.805

27. Lee HY, Mohammed KA, Kaye F, Sharma P, Moudgil BM, Clapp WL, Nasreen N: Targeted delivery of let-7a microRNA encapsulated ephrin-A1 conjugated liposomal nanoparticles inhibit tumor growth in lung cancer. *Int J Nanomedicine* 8:4481-94 (2013)
No doi was found.

28. Chen G, Umelo IA, Lv S, Teugels E, Fostier K, Kronenberger P, Dewaele A, Sadones J, Geers C, De Grève J: miR-146a inhibits cell growth, cell migration and induces apoptosis in non-small cell lung cancer cells. *PLoS One* 8(3):e60317 (2013)
DOI: 10.1371/journal.pone.0060317

29. Park S, Minai-Tehrani A, Xu CX, Chang SH, Woo MA, Noh MS, Lee ES, Lim HT, An GH, Lee KH, Sung HJ, Beck GR, Cho MH: Suppression of A549 lung cancer cell migration by precursor let-7g microRNA. *Mol Med Rep* 3(6):1007-13 (2010)
No doi was found.

30. Wang G, Mao W, Zheng S: MicroRNA-183 regulates Ezrin expression in lung cancer cells. *FEBS Lett* 582(25-26):3663-8 (2008)
DOI: 10.1016/j.febslet.2008.09.051

31. Hu H, Li S, Liu J, Ni B: MicroRNA-193b modulates proliferation, migration, and invasion of non-small cell lung cancer cells. *Acta Biochim Biophys Sin (Shanghai)* 44(5):424-30 (2012)
DOI: 10.1093/abbs/gms018

32. Ma Q, Jiang Q, Pu Q, Zhang X, Yang W, Wang Y, Ye S, Wu S, Zhong G, Ren J, Zhang Y, Liu L, Zhu W: MicroRNA-143 inhibits migration and invasion of human non-small-cell lung cancer and its relative mechanism. *Int J Biol Sci* 9(7):680-92 (2013)
DOI: 10.7150/ijbs.6623

33. Luo W, Huang B, Li Z, Li H, Sun L, Zhang Q, Qiu X, Wang E: MicroRNA-449a is downregulated in non-small cell lung cancer and inhibits migration and invasion by targeting c-Met. *PLoS One* 8(5):e64759 (2013)
DOI: 10.1371/journal.pone.0064759

34. Zhao B, Han H, Chen J, Zhang Z, Li S, Fang F, Zheng Q, Ma Y, Zhang J, Wu N, Yang

Y: MicroRNA let-7c inhibits migration and invasion of human non-small cell lung cancer by targeting ITGB3 and MAP4K3. *Cancer Lett* 342(1):43-51 (2014)
DOI: 10.1016/j.canlet.2013.08.030

35. Yongchun Z, Linwei T, Xicai W, Lianhua Y, Guangqiang Z, Ming Y, Guangjian L, Yujie L, Yunchao H: MicroRNA-195 inhibits non-small cell lung cancer cell proliferation, migration and invasion by targeting MYB. *Cancer Lett* pii: S0304-3835(14)00055-X (2014)
No doi was found.

36. Shi SJ, Zhong ZR, Liu J, Zhang ZR, Sun X, Gong T: Solid lipid nanoparticles loaded with anti-microRNA oligonucleotides (AMOs) for suppression of microRNA-21 functions in human lung cancer cells. *Pharm Res* 29(1):97-109 (2012)
DOI: 10.1007/s11095-011-0514-6

37. Wang HB, Zhang HJ, Su JM, Zhou WY, Wang HY, Chen XF: Epithelial-mesenchymal transition (EMT) and its effect on microRNA expression in lung cancer. *Zhonghua Zhong Liu Za Zhi* 33(8):590-3 (2011)
No doi was found.

38. Lin CW, Chang YL, Chang YC, Lin JC, Chen CC, Pan SH, Wu CT, Chen HY, Yang SC, Hong TM, Yang PC: MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. *Nat Commun* 4:1877 (2013)
DOI: 10.1038/ncomms2876

39. Chen LT, Xu SD, Xu H, Zhang JF, Ning JF, Wang SF: MicroRNA-378 is associated with non-small cell lung cancer brain metastasis by promoting cell migration, invasion and tumor angiogenesis. *Med Oncol* 29(3):1673-80 (2012)
DOI: 10.1007/s12032-011-0083-x

40. Arora S, Ranade AR, Tran NL, Nasser S, Sridhar S, Korn RL, Ross JT, Dhruv H, Foss KM, Sibenaller Z, Ryken T, Gotway MB, Kim S, Weiss GJ: MicroRNA-328 is associated with (non-small) cell lung cancer (NSCLC) brain metastasis and mediates NSCLC migration. *Int J Cancer* 129(11):2621-31 (2011)
DOI: 10.1002/ijc.25939

41. Lee JG, Lee CY, Park IK, Kim DJ, Park SY, Kim KD, Chung KY: Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. *Ann Thorac Surg* 85(1):211-5 (2008)
DOI: 10.1016/j.athoracsur.2007.08.020

42. Roth C, Kasimir-Bauer S, Pantel K, Schwarzenbach H: Screening for circulating nucleic acids and caspase activity in the peripheral blood as potential diagnostic tools in lung cancer. *Mol Oncol* 5(3):281-91 (2011)
DOI: 10.1016/j.molonc.2011.02.002

43. Wang R, Wang ZX, Yang JS, Pan X, De W, Chen LB: MicroRNA-451 functions as a tumor suppressor in human non-small cell lung cancer by targeting ras-related protein 14 (RAB14) *Oncogene* 30(23):2644-58 (2011)
DOI: 10.1038/onc.2010.642

44. Donnem T, Fenton CG, Lonvik K, Berg T, Eklo K, Andersen S, Stenvold H, Al-Shibli K, Al-Saad S, Bremnes RM, Busund LT: MicroRNA signatures in tumor tissue related to angiogenesis in non-small cell lung cancer. *PLoS One* 7(1):e29671 (2012)
DOI: 10.1371/journal.pone.0029671

45. Wu C, Cao Y, He Z, He J, Hu C, Duan H, Jiang J: Serum Levels of miR-19b and miR-146a as Prognostic Biomarkers for Non-Small Cell Lung Cancer. Tohoku J Exp Med 232(2):85-95 (2014)
DOI: 10.1620/tjem.232.85

46. Xu T, Liu X, Han L, Shen H, Liu L, Shu Y: Up-regulation of miR-9 expression as a poor prognostic biomarker in patients with non-small cell lung cancer. *Clin Transl Oncol*. (2013) (Epub ahead of print)
DOI: 10.1007/s12094-013-1106-1

47. Li ZH, Zhang H, Yang ZG, Wen GQ, Cui YB, Shao GG: Prognostic significance of serum microRNA-210 levels in nonsmall-cell lung cancer. *J Int Med Res* 41(5):1437-44 (2013)
DOI: 10.1177/0300060513497560

48. Stenvold H, Donnem T, Andersen S, Al-Saad S, Valkov A, Pedersen MI, Busund LT, Bremnes RM: High tumor cell expression of microRNA-21 in node positive non-small cell lung cancer predicts a favorable clinical outcome. *BMC Clin Pathol* 14(1):9 (2014)
DOI: 10.1186/1472-6890-14-9

49. Liu H, Chen X, Gao W, Jiang G: The expression of heparanase and microRNA-1258 in human non-small cell lung cancer. *Tumour Biol* 33(5):1327-34 (2012)

DOI: 10.1007/s13277-012-0380-9

50. Wang G, Mao W, Zheng S, Ye J: Epidermal growth factor receptor-regulated miR-125a-5p--a metastatic inhibitor of lung cancer. *FEBS J* 276(19):5571-8 (2009)
DOI: 10.1111/j.1742-4658.2009.07238.x

51. Xu L, Wen Z, Zhou Y, Liu Z, Li Q, Fei G, Luo J, Ren T: MicroRNA-7-regulated TLR9 signaling-enhanced growth and metastatic potential of human lung cancer cells by altering the phosphoinositide-3-kinase, regulatory subunit 3/Akt pathway. *Mol Biol Cell* 24(1):42-55 (2013)
DOI: 10.1091/mbc.E12-07-0519

52. Yang WB, Chen PH, Hsu T 1st, Fu4 TF, Su WC, Liaw H, Chang WC, Hung JJ: Sp1-mediated microRNA-182 expression regulates lung cancer progression. *Oncotarget*. (2014) (Epub ahead of print)
No doi was found.

53. Kuo PL, Liao SH, Hung JY, Huang MS, Hsu YL: MicroRNA-33a functions as a bone metastasis suppressor in lung cancer by targeting parathyroid hormone related protein. *Biochim Biophys Acta* 1830(6):3756-66 (2013)
DOI: 10.1016/j.bbagen.2013.02.022

54. Ceppi P, Mudduluru G, Kumarswamy R, Rapa I, Scagliotti GV, Papotti M, Allgayer H: Loss of miR-200c expression induces an aggressive, invasive, and chemoresistant phenotype in non-small cell lung cancer. *Mol Cancer Res* 8(9):1207-16 (2010)
DOI: 10.1158/1541-7786.MCR-10-0052

55. Yang Y, Liu L, Zhang Y, Guan H, Wu J, Zhu X, Yuan J, Li M: MiR-503 targets PI3K p85 and IKK-β and suppresses progression of non-small cell lung cancer. *Int J Cancer* (2014) (Epub ahead of print)
DOI: 10.1002/ijc.28799

56. Kumarswamy R, Mudduluru G, Ceppi P, Muppala S, Kozlowski M, Niklinski J, Papotti M, Allgayer H: MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snai1 and is downregulated in non-small cell lung cancer. *Int J Cancer* 130(9):2044-53 (2012)
DOI: 10.1002/ijc.26218

57. Carver EA, Jiang R, Lan Y, Oram KF, Gridley T: The mouse snail gene encodes a key regulator of the epithelial-mesenchymal transition. *Mol Cell Biol* 21(23):8184-8 (2001)
DOI: 10.1128/MCB.21.23.8184-8188.2001

58. Olmeda D, Jorda M, Peinado H, Fabra A, Cano A: Snail silencing effectively suppresses tumour growth and invasiveness. *Oncogene* 26:1862–74 (2007)
DOI: 10.1038/sj.onc.1209997

59. Roy HK, Iversen P, Hart J, Liu Y, Koetsier JL, Kim Y, Kunte DP, Madugula M, Backman V, Wali RK: Down-regulation of SNAIL suppresses MIN mouse tumorigenesis: modulation of apoptosis, proliferation, and fractal dimension. *Mol Cancer Ther* 3:1159–65 (2004)
No doi was found.

60. Yu T, Li J, Yan M, Liu L, Lin H, Zhao F, Sun L, Zhang Y, Cui Y, Zhang F, Li J, He X, Yao M: MicroRNA-193a-3p and -5p suppress the metastasis of human non-small-cell lung cancer by downregulating the ERBB4/PIK3R3/mTOR/S6K2 signaling pathway. *Oncogene* (2014) (Epub ahead of print)
DOI: 10.1038/onc.2013.574

61. Liu J, Lu KH, Liu ZL, Sun M, De W, Wang ZX: MicroRNA-100 is a potential molecular marker of non-small cell lung cancer and functions as a tumor suppressor by targeting polo-like kinase 1. *BMC Cancer* 12:519 (2012)
DOI: 10.1186/1471-2407-12-519

62. Li Y, Jiang Q, Xia N, Yang H, Hu C: Decreased expression of microRNA-375 in nonsmall cell lung cancer and its clinical significance. *J Int Med Res* 40(5):1662-9 (2012)
DOI: 10.1177/030006051204000505

63. Li J, Song Y, Wang Y, Luo J, Yu W: MicroRNA-148a suppresses epithelial-to-mesenchymal transition by targeting ROCK1 in non-small cell lung cancer cells. *Mol Cell Biochem* 380(1-2):277-82 (2013)
DOI: 10.1007/s11010-013-1682-y

64. Pacurari M, Addison JB, Bondalapati N, Wan YW, Luo D, Qian Y, Castranova V, Ivanov AV, Guo NL: The microRNA-200 family targets multiple non-small cell lung cancer prognostic markers in H1299 cells and BEAS-2B cells. *Int J Oncol* 43(2):548-60 (2013)
No doi was found.

65. Yang J, Liu H, Wang H, Sun Y: Down-regulation of microRNA-181b is a potential prognostic marker of non-small cell lung cancer. *Pathol Res Pract* 209(8):490-4 (2013)
DOI: 10.1016/j.prp.2013.04.018

Abbreviations: NSCLC, Non-small cell lung cancer; miRNAs, microRNAs; 3'-UTR, 3'-untranslated region; MTA1, metastasis-associated gene 1

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