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...
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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-101 by targeting CD44v3, miR-449a by targeting c-Met, miR-let-7c by targeting ITGB3 and MAP4K3, 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...
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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.

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7. REFERENCES

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

**Key Words:** Non-Small Cell Lung Cancer, MicroRNAs, Metastasis, Review

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