Editorial

From biological mechanisms to clinical implications: the role of mineral dust-induced gene in lung cancers

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While lung cancer has been a leading cause of death for humans with highest morbidity among all types of cancers, air pollution poses an increasing impact on the incidence of this catastrophe (1-3). Mineral dust-induced gene (*Mdig*) is a lung cancer-related gene found in alveolar macrophages from coal miners exposed to mineral dusts in 2005 (4). It was later confirmed to be the same gene as the myc-induced nuclear antigen with an estimated molecular weight of 53 kDa (mina53) (5) and also the nuclear protein 52 (NO52) (6). Mdig/mina53 is located on chromosome 3 within a single open reading frame of 465 amino acids (4,5), and chiefly expressed in the cellular nuclei with part of the protein condensed in the nucleolus (5-7). However, the intracellular distribution of Mdig/mina53 may vary with cell cycle phases and different extracellular environments (8). In normal individuals, Mdig/mina53 is expressed in the liver, skeletal muscle, heart, pancreas and placenta, but not in lungs (4). When localized in lungs, therefore, Mdig/mina53 might represent a potential target for future therapy. Below we present an update on understanding of biological behaviors of Mdig/mina53 related to lung cancers.

Histone demethylase

Epigenetic alterations in histones resulting from the actions of histone demethylases play an important role in carcinogenesis. It has been found that all JmjC domain-containing proteins exhibit effects of histone demethylase (9). Interestingly, human *Mdig/mina53* gene encodes a protein with a conserved JmjC domain (4). Destruction of this domain is associated with deactivation of Mdig proteins, indicating that the JmjC domain is the essence of Mdig (7).

The level of histone H3 lysine 9 trimethylation (H3K9me3) seems critical in the production and maintenance of heterochromatin in that a reduction in H3K9me3 may lead to gene instability and tumorigenesis (10). Chen *et al.* (11) found that Mdig/mina53 was involved in H3K9me3 demethylation, and that the overexpression of Mdig/mina53 in A549 cells decreased the heterochromatin conformation of cells and caused a significant reduction of H3K9me3 in the promoter region of H19 while total H3K9me3 decreased slightly. Few changes were observed for H3K27me3, H3K36me3 and H3K4me3. Lu *et al.* (12) also showed that Mdig/mina53 was involved in the demethylation of H3K9me3 and facilitated ribosomal RNA synthesis through H3K9me3 demethylation. These studies suggest that Mdig/mina53 is essential in mediating histone demethylation and heterochromatin conformation, which might be one of the important behaviors linking *Mdig/mina53* gene to tumorigenesis and genomic instability.

Hydroxylation of ribosomal protein

Ribosome biogenesis is one of the essential components during cell proliferation. Oxygenase catalyzes hydroxylation of ribosomal proteins which regulate gene transcriptions (13). It is suggested that oxygenases also catalyze demethylation of N-ε-methyllysine histone residues (JmjC demethylases) (14) and lysyl 5-hydroxylation of splicing-related proteins (JMJD6) (15). Mdig/mina53 interacts with various ribosomal proteins and is involved in ribosome biogenesis (6) and ribosomal RNA transcription (12). It was confirmed

that Mdig/mina53 belongs to the a ribosomal oxygenases family and could catalyze histidyl hydroxylation of the ribosomal protein Rpl27a which is an important subunit of the 60S ribosome for protein translation (13). More than 90% of the ribosomal protein Rp127a was found in the form of hydroxylation in human lung adenocarcinoma A549 cells, embryonic kidney cells and Hodgkin lymphoma tissues.

Immune response

The Th1 response may lead to cell-mediated immunity whereas Th2 response is characterized by the production of IL-4, resulting in the activation of B-cells associated with humoral immunity. It was found that Mdig/mina53 could be recruited to IL-4 promoter through NFAT (nuclear factor of activated T cells) transcription factor (16).

Mori *et al.* (17) reported that Mdig/mina53 has a great impact on allergic asthmatic response by regulating the allergic response via IL-4 production in an allergic asthma model. They found airway hyperresponsiveness to methacholine in wild-type mice but not in Mdig/mina53-deficient mice after challenging with house dust mite allergens. However, the number of immune cells including eosinophils and levels of IL-4 and IL-5 produced by Th2 cells in BALF from the Mdig/mina53-deficient mice was lowered compared with the wild-type mice. These results suggested that Mdig/mina53 might have an effect on the immune response by modulating the production of IL-4.

Tumorigenicity

Overexpressed Mdig/mina53 was found in lung cancer tissues and human lung cancer cell lines, suggesting that Mdig/mina53 may be associated with carcinogenesis (4). Lu *et al.* (12) demonstrated that overexpression of Mdig/mina53 in lung cancer tissues was a common feature of non-small cell lung cancer. Moreover, Mdig/mina53 was involved in demethylation of H3K9me3 and resulted in an increase in ribosomal RNA expression. These strongly suggest that Mdig/mina53 exhibited oncogenic property through antagonizing H3K9me3 and could facilitate ribosomal RNA synthesis (12). Studies also indicate that Mdig/mina53 is frequently expressed in human lung cancers and exhibits oncogenic property in NIH 3T3 cells (7). Lu *et al.* (12) reported that Mdig/mina53 contributed to the development and progression of human lung cancer through altering histone H3 methylation. All these findings suggest that Mdig/mina53 participates in genomic instability and lead to the development of cancers.

Regulation of cell cycle and cell proliferation

It has been found that silencing Mdig/mina53 mRNA expression in A549 lung cancer cells suppresses cell proliferation by delaying the cell cycle transition from G1 to S phase (4,18). These results indicate that Mdig/mina53 might promote cell proliferation by regulating the G1/S transition. The G1/S transition is a key checkpoint in the cell cycle and deregulation of cell cycle components may lead to tumor formation (19). $p27^{KIP1}$, one of cell cycle-related genes that acts as a tumor suppressor in humans (20), has a negative effect on regulating the cell cycle by inhibiting the G1 phase kinase complexes (such as cyclin e-cdk2 and d-cdk4). Study by Ma *et al.* (18) found that knockdown of Mdig/mina53 in A549 cells can increase the levels of $p27^{KIP1}$ on both mRNA and protein, indicating that Mdig/mina53 is a negative regulator for the major cell cycle checkpoint protein, $p27^{KIP1}$. Furthermore, the phosphorylation of $p27^{KIP1}$ at its Thr187 site was also inhibited. Importantly, Ma *et al.* (18) also found that upregulation of Mdig/mina53 was accompanied by downregulation of $p27^{KIP1}$ in both lung cancer tissues and bronchial stump. This suggests that Mdig/mina53 play an essential role in the cell cycle regulation, cell proliferation and tumor formation by inhibiting $p27^{KIP1}$ expression through the phosphorylation of its Thr187 site.

Invasion and metastasis of cancer cells

Rapid proliferation, invasion and migration *in vivo* are the primary characters of tumor cells. Several oncogenic signals play majorly as proliferative elements for cancer cell growth, in contrast, others might mainly contribute to the metastasis or invasiveness of the cancer cells. In the early phase of carcinogenesis, unremitting proliferation would be pivotal for the formation of discernible cancer. During the development of cancer, heterogeneous cancer cell sub-clones will be generated by genetic and epigenetic evolution of new cancer cell lineages that could supply the tumor cells and disseminate those tumor cells to distant sites (21).

Yu *et al.* (8) illuminated the contradictory roles of Mdig/mina53 about lung cancer A549 cell proliferation, migration and invasion, i.e., the overexpression of Mdig/mina53 advanced A549 cell proliferation but checked cell

migration/invasion. To discuss whether those findings are clinically relevant to lung cancer patients, Yu *et al.* detected the expression levels of Mdig/mina53 and analyzed the survival data, which pooled 1,715 patients with lung cancer basing on an online gene profiling database and grouped them according to the levels of Mdig/mina53 expression. The analysis displayed a negative correlation between the overall survival and Mdig/mina53 expression levels in the patients, such that higher expression levels of Mdig/mina53 was correlated with poorer overall survival of the patients with lung cancer. While, when the lung cancer patients were categorized based on the American Joint Committee on Cancer (AJCC) staging of lymph node (N) metastasis status, it was observed that the higher levels of Mdig/mina53 expression were associated to poorer overall survival in those with AJCC N0 (no regional lymph node metastasis) and AJCC N1 (possible proximal lymph node metastasis) lung cancer. Although not statistically significant, the higher levels Mdig/mina53 expression tended to predict better overall survival rather than poorer overall survival of the AJCC N2 patients, which might be explained by the inhibitory effects of Mdig/mina53 against the migration and invasion of cancer cells.

However, Komiya *et al.* (22) showed that Mdig/mina53 overexpression might be correlated with favorable prognosis of the lung cancer patients, particularly for the patients with stage I lung cancer. The inconsistency between Yu *et al.* (8) and Komiya *et al.* (22) might be caused by the ethnic disparity and discrepancy in sample size of the study population.

In summary, the exact mechanisms underlying the role of Mdig/mina53 in tumor invasion and metastasis remain currently unclear. How Mdig gene regulates body immune response needs to be fully elucidated, since few studies were conducted with animal models investigating the mechanisms of Mdig gene. Establishment of a comprehensive research system of molecular biology-cytology-animal model is expected. In combination with studies on solid tumors samples, researchers may find out the specific biological effects and regulatory mechanisms of Mdig gene, which is helpful to develop new approach in controlling and treating human malignancy (23).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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