ADAM9-associated microRNA suppression promotes lung cancer progression

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Background: Lung cancer is the leading cause of cancer death worldwide, and metastasis is a major cause of morbidity and mortality in lung cancer. A disintegrin and metalloprotease 9 (ADAM9) is a member of the ADAM family of type I transmembrane proteins and plays an important role in cell adhesion and migration. Overexpression of ADAM9 is observed in many cancers and correlates with lung cancer brain metastasis. In our previous study, we demonstrated that ADAM9 promotes lung cancer metastasis via inducing oncogenic protein CDCP1 expression; however, the regulated process remains unclear.

Methods: We have performed a genome-wide approach to screen ADAM9-associated mRNAs and microRNAs involved in metastasis by comparing our established brain-metastatic lung cancer sublines and their parental cancer cells. Clinical lung adenocarcinoma samples were included to investigate the clinical relevance of ADAM9-associated microRNAs. The effects of rescued microRNAs for suppressing lung cancer progression were also evaluated.

Results: We identified that CDCP1, was up-regulated by ADAM9 in brain-metastatic lung cancer sublines, and the 3'UTR of *CDCP1* contains the predicted binding sites of several microRNAs that were down-regulated in ADAM9-overexpressed cancer cells. Luciferase assays and western blot analysis showed that *CDCP1* is a target gene of microRNAs. The up-regulation of microRNAs, in turn, reduced the expression of its target gene and further inhibited the migration ability of aggressive lung adenocarcinoma cells. CDCP1 protein level was decreased in exogenous expression of microRNAs. Induction of microRNAs inhibited tumor cell mobility,

anchorage-free survival and tumor-initiating cell formation *in vitro* and delayed tumor metastases in animals.
Conclusion: This study revealed that *ADAM9* activates *CDCP1* through the release of microRNA inhibition of *CDCP1* in lung adenocarcinoma and plays a role in lung cancer metastasis.

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Key words: ADAM9; CDCP1; lung adenocarcinoma