ADAM9 regulates microRNAs expression for lung cancer metastasis

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Lung cancer is the leading cause of cancer death worldwide, and metastasis is a major cause of morbidity and mortality in lung cancer. We demonstrated *ADAM9* (a disintegrin and metalloprotease 9) was overexpressed in lung metastatic tumor tissues and was associated with a poor outcome in lung cancer patients. Knocking down *ADAM9* expression in lung cancer cells showed significant reduction of lung cancer metastasis *in vitro and in vivo*. We identified that ADAM9 enhanced the expression of the pro-migratory protein CDCP1 to promote lung metastasis; however, the regulatory process remains unknown. Because microRNAs regulate many biological functions and disease processes (e.g., cancer) by down-regulating their target genes, microRNA microarrays were used to identify ADAM9-regulated miRNAs that target CDCP1 in aggressive lung cancer cells. We found that endogenous miR-218, which is abundant in normal lung tissue but suppressed in lung tumors, was regulated during the process of ADAM9-mediated CDCP1 expression. Furthermore, 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 miR-218. Induction of miR-218 inhibited tumor cell mobility, anchorage-free survival, and tumor-initiating cell formation *in vitro* and delayed tumor metastases in mice. Our findings reveal an integrative tumor suppressor function of miR-218 in lung cancer and further suggest that restoring miR-218 expression could be a potential therapeutic regimen in preventing lung cancer metastasis.