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ADAM9 regulates microRNAs expression for lung cancer metastasis

Short Title:
ADAM9 regulates microRNAs

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Abstract:
Lung cancer is the leading cause of cancer death worldwide, and brain metastasis is a major cause of morbidity and mortality in lung cancer. Currently, it is not clear which molecules or what mechanisms mediate lung cancer brain metastasis. To explore this question, we compared our established brain-metastatic lung cancer sublines with their parental cancer cells, and identified ADAM9 (a disintegrin and metalloprotease 9) was overexpressed in metastatic sublines. Knocking down ADAM9 expression in lung cancer cells also showed significant reduction of lung cancer brain metastasis in vitro and in vivo. Furthermore, using a genome-wide approach to screen ADAM9-related mRNAs and microRNAs involved in brain metastasis, we identified that CDH2, encoding N-cadherin, was up-regulated by ADAM9 in brain-metastatic lung cancer sublines, and the 3'UTR of CDH2 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 CDH2 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. This study revealed that ADAM9 activates CDH2 through the release of microRNA inhibition of CDH2 in lung adenocarcinoma and plays a role in lung cancer metastasis.
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