ADAM9 coordinates genes in anoikis resistance for lung cancer metastases

Yuh-Pyng Sher[1,2]*, Chen-Yuan Lin[1,2,3], Cheng-Chung Huang[1,2], Liang-Chuan Lai[4], Ting-Ting Kuo[1,2], Guan-Chin Tseng[5], and Mien-Chie Hung[2, 6]

[1]Graduate Institute of Clinical Medical Science, China Medical University, Taichung 404, Taiwan
[2]Center for Molecular Medicine, [3]Division of Hematology and Oncology,
[4]Graduate Institute of Physiology, National Taiwan University, Taipei, Taiwan [5]Department of Pathology, China Medical University Hospital, Taichung 404, Taiwan
[6]Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA

Background:

Brain 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. However, the molecular mechanism is not clearly understood.

Material and methods

By comparing our established brain-metastatic lung cancer sublines and their parental cancer cells, we found ADAM9 (a disintegrin and metalloprotease 9) was overexpressed in metastatic sublines. To further understand the mechanisms by which ADAM9 promotes lung cancer brain metastasis in addition to its role in brain endothelial cell adhesion, we analyzed the differential gene expression between control and ADAM9 knockdown brain metastatic lung cancer cells and investigated the ADAM9-related pathways required for lung cancer brain metastasis. Lung adenocarcinoma patient samples were also used to investigate the clinical relevance of ADAM9.

Results:

A transcriptome microarray analysis reveals a set of genes that are associated with ADAM9 such as CDCP1, a regulator of anoikis resistance. We demonstrate ADAM9 enhances active form of CDCP1 via tPA activation for cell metastasis. Blocking ADAM9-mediated downstream signaling offers a synergistic cytotoxic effect in lung cancer cells. Analysis of clinical samples shows that patients with high level of these genes and ADAM9 correlate with poor prognosis. Therefore, ADAM9 regulates a complicated network in lung cancer brain metastasis through tPA-mediated CDCP1 cleavage.

Conclusions:

The primary cause of death for most cancer patients' metastases, and the most common primary malignancy that gives rise to brain metastases is lung cancer. The current study provides critical insights into the mechanism of lung cancer brain metastasis through ADAM9-regulated CDCP1 activation via tPA-mediated CDCP1 cleavage and may have therapeutic value for lung cancer patients with metastasis.