ADAM9 mediated inflammation for lung cancer metastasis

Yuh-Pyng Sher, Chen-Yuan Lin, Liang-Chuan Lai, Tzu-Pin Lu, Hung-Jen Chen, Guan-Chin Tseng, and Mien-Chie Hung
Graduate Institute of Clinical Medical Science, Center for Molecular Medicine, China Medical University & Hospital, Taichung 404, Taiwan

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, especially how cancer cells penetrate the tight structure of the blood–brain barrier (BBB). 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. As evident from clinical samples, we observed high expression levels of ADAM9 in the primary lung tumor tissue of NSCLC patients who also have significantly high ADAM9 level in their paired brain or bone-metastatic tumor tissues, suggesting that ADAM9 likely plays an important role in lung cancer metastasis. Knocking down ADAM9 expression in lung cancer cells significantly reduced lung cancer brain metastasis *in vitro and in vivo*. Using a genome-wide approach to screen ADAM9-related molecules involved in metastasis, we found that many adhesion molecules and proteins associating in inflammation potentially are up-regulated by ADAM9 in brain-metastatic lung cancer sublines. To analyze the interactive pathways that reflect the relationships for the genes regulated by ADAM9 in Ingenuity Pathways Analysis, several pathways in cytokines expression, cell to cell signaling, communication between innate and adaptive immune cells, and cell-mediated immune response are significantly altered, suggesting that inflammation plays important roles in ADAM9 mediated cancer cells metastasis.

Acknowledgment: Grant support from NSC99-2314-B-039-029-MY3.