

ORAL PRESENTATION

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Spontaneous development of lung adenocarcinoma in the *CADM1* gene-deficient mice

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Aberration of cell adhesion is a critical step in the development and progression of human tumors. A tumor suppressor gene, *CADM1* (Cell adhesion molecule 1)/*TSLC1* (Tumor suppressor in lung cancer 1), was originally identified in non-small cell lung cancer (NSCLC) by its tumor suppressor activity in nude mice. *CADM1* encodes an immunoglobulin superfamily cell adhesion molecule which is expressed in the brain, testis, lung and various other epithelial tissues. In normal polarized epithelia, *CADM1* is expressed along the lateral membrane and associates in the cytoplasm with a member of 4.1-family proteins carrying actin-binding activity. On the other hand, *CADM1* is inactivated by loss of the chromosomal fragment and/or methylation of the gene promoter in 30–60% of various human cancers, including NSCLC. To understand the physiological roles of *CADM1*, we have generated *Cadm1/Tslc1* gene-deficient mice and have found that *Cadm1*^{-/-} male mice are infertile due to the disruption of cell adhesion between the immature spermatocytes and Sertoli cells.

Here, we demonstrate that more than 30% of *Cadm1*^{-/-} mice developed lung adenomas or adenocarcinomas spontaneously at 15 months of age. In the tumors, normal alveolar structure was completely replaced by the tumor cells with atypical nuclei. Lung tumors also developed in *Cadm1*^{+/-} mice at 18 months of age through the second hit of the *Cadm1* gene, indicating that *CADM1* cascade is critical to lung tumor suppression. Immunohistochemical study revealed that the membrane localization of 4.1N and *CADM4*,

another member of *CADM* family proteins expressed in the lung, was abrogated in the tumors but not in the normal epithelia. These results suggest that the disruption of the *CADM-4.1* cascade of cell adhesion is prerequisite to lung tumor formation.

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