News Release

Title

CD109 regulates *in vivo* tumor invasion in lung adenocarcinoma through TGF-β signaling

Key Points

- Researchers identified a protein called CD109 as a crucial regulator of stromal invasion in lung adenocarcinoma.
- CD109 is expressed preferentially in invasive lesions of lung adenocarcinoma, suggesting that CD109 is a histological marker of stromal invasion.
- They discovered a novel interaction between CD109 and LTBP1 in activating TGF-β signaling, which may explain the mechanism of stromal invasion in lung adenocarcinoma.

Summary

Stromal invasion is considered an important prognostic factor in patients with lung adenocarcinoma. The mechanisms underlying the formation of tumor stroma and stromal invasion have been studied in the lung; however, they are still unclear.

A research group at Nagoya University identified an association between higher expression of a cancer-related protein CD109 in human lung adenocarcinoma and a significantly worse prognosis, according to immunohistochemical analysis. The group showed that CD109 deficiency significantly reduced the area of stromal invasive lesions in a genetically engineered CD109-deficient lung adenocarcinoma mouse model, which correlated to the results observed in human lung adenocarcinoma. Furthermore, they identified latent TGF-β binding protein-1 (LTBP1) as a CD109-interacting protein using mass spectrometry and confirmed their interaction by co-immunoprecipitation. Importantly, increased CD109 expression enhanced stromal TGF-β activation in the presence of LTBP1. Therefore, these data suggest the significance of the regulation of TGF-β signaling through CD109 and LTBP1 interaction in tumor stroma, and also reveal the importance of CD109 expression levels in promoting the lung cancer cell proliferation, migration, and invasion, and thus predicting the outcome of patients suffering from lung adenocarcinoma. Therefore, CD109 protein could be a potential therapeutic target for this disease.

Research Background

Stromal invasion is the first stage in the process of metastatic lesion development. It is one of the most important prognostic factors in cancer. However, the mechanism underlying stromal invasion remains unclear. Besides, despite the importance of invasive size to determine the clinical stage in lung adenocarcinoma, there is no good histological marker of stromal invasion in lung adenocarcinoma.

Research Results

To investigate the mechanism of invasion in lung adenocarcinoma, a research group at Nagoya University performed studies using human lung adenocarcinoma tissues, and identified the expression of a protein called CD109 preferentially in invasive lesions. Histological investigation revealed that the patients who had a higher level of CD109 expression exhibited larger invasive tumor size and poorer prognosis. In an autochthonous lung adenocarcinoma mouse model, the group showed CD109 deficiency significantly reduced the area of invasive lesions which corresponded to the results observed in human lung adenocarcinoma. In addition, they conducted in vitro assay, which verified CD109 enhanced invasive capacity in lung adenocarcinoma cells. All these findings reveal the significance of CD109 in invasive growth of lung adenocarcinoma.

Furthermore, they showed that lung adenocarcinoma with high CD109 expression exhibited extensive stromal desmoplasia. By performing a large scale co-immunoprecipitation, they isolated latent TGF-ß binding protein 1 (LTBP1) as a CD109-interacting protein. LTBP1 is a stromal protein which mediates TGF-ß activation, an event essential for developing pro-cancerous microenvironment including stromal desmoplasia. Finally, TGF-ß bioassay demonstrated that CD109 promotes TGF-ß activation in the presence of LTBP1, describing the mechanistic role of CD109-LTBP1 interaction in stromal desmoplasia.

Research Summary and Future Perspective

The present study describes a mechanism responsible for invasion of lung adenocarcinoma, and suggests that targeting CD109 could be a potential therapeutic approach for lung adenocarcinoma.

In addition, interobserver variability in measuring the size of invasive lesions is often a challenge among pathologists especially in lung adenocarcinoma. This study also addressed this issue in pathological practice by indicating that CD109 could be a good histological marker of invasive lesions.

Publication

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