論 文 要 旨

High filamin-C expression predicts enhanced invasiveness and poor outcome in glioblastoma multiforme

（膠芽腫における filamin C の高発現は、
腫瘍細胞の高浸潤能と臨床的転帰不良を示唆する）

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Glioblastoma multiforme (GBM), the most common brain malignancy in adults, is generally aggressive and incurable, even with multiple treatment modalities and agents. GBM progression is associated with several biological and biochemical changes, including cell shape transformation, enhanced mobility and ability to degrade extracellular matrix (ECM), and the emergence of a stem cell phenotype. Filamins (FLNs) are a group of actin-binding proteins that regulate the actin cytoskeleton in cells. The three members of the FLN family (FLNA, FLNB, and FLNC) are encoded by different genes and share 60–80% amino acid identity overall and 45% identity in the two hinge regions. Base on The Cancer Genome Atlas (TCGA) data portal, which conduct Kaplan Meier survival curve analysis of GBM patients samples on FLN family gene expression, showed that only FLNC has a significant result in survival analysis study on GBM, not FLNA nor FLNB. However, the role of FLNs , especially FLNC, in malignancies—particularly in GBM—is unclear.

Methods

The relation between FLNC expression and overall survival in GBM was evaluated by the Kaplan−Meier analysis using GBM patients from the Kagoshima University Hospital (n=90) and data from the Cancer Genome Atlas (TCGA) (n=153). To assess FLNC function in GBM, cell migration and invasion were examined with Transwell and Matrigel invasion assays using FLNCoverexpressing U251MG and LN299 GBM cells, and ShRNA-mediated FLNC knocked-down KNS81 and U87MG cells. The gelatin zymography assay was used to estimate matrix metalloproteinase (MMP) 2 activity.

Result

In silico analysis of GBM patient data from TCGA and immunohistochemical analyses of clinical GBM specimens revealed that increased FLNC expression was associated with poor patient prognosis. However, FLNA and FLNB expression levels were unrelated to prognosis. A univariate and multivariate Cox proportional hazards analysis showed chemotherapy, radiotherapy, EOR degree and FLNC expression are independent prognostic factors in both of TCGA and our clinical data.

In vitro, FLNC overexpression in GBM cell lines was positively correlated with enhanced invasiveness, but not migration. The result of MMP2 zymography assay to determine the role of FLNC to remodeling ECM suggest that FLNC enhances the ability of GBM cells to invade the surrounding ECM by inducing MMP2 activation.

Conclusion

Our findings show that high FLNC expression in GBM patients is an independent predictor of unfavorable prognosis and that FLNC increases the invasive potential of GBM via regulation of MMP2 expression and activity. Thus, FLNC is a useful biomarker and a promising therapeutic target in GBM. Identification of FLNC-interacting proteins and downstream signaling pathways will be critical for elucidating its function in future studies and in in vivo experiments.

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