FE65 in breast cancer: its clinicopathological and biological significance

（書式１８）

学　位　論　文　要　約
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博士論文題目 Title of dissertation

FE65 in breast cancer: its clinicopathological and biological significance

(乳癌細胞における Fe65 発現の生物学的／臨床的意義の検討)

東北大学大学院医学系研究科　専攻

病理病態学　講座　病理診断学　分野

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Background

Transcription coregulator adapter protein FE65 has been well known to play pivotal roles in pathogenesis of Alzheimer's disease by regulating the processing of amyloid precursor protein (APP). In addition to Alzheimer's disease, APP was also recently reported to be involved in development of human malignancies. Therefore, in this study, I explored the status of FE65 in different subtypes of human breast cancer and correlated the results with cell proliferation and migration of carcinoma cells and individual clinicopathological factors of the patients to examine its biological and clinical significance in breast cancer.

Methods

I first immunolocalized FE65 in breast cancer cases and correlated the results with their tumor grades. I then explored the findings using proximity ligation assay, WST-8 and wound healing assay. The RT2 Profiler Human PCR Array Human Estrogen Receptor (ER) Signaling was also used to profile 96 ER related key genes. Hoechst 33342 Staining and Evaluation was used to evaluate apoptosis.

Results

FE65 immunoreactivity in carcinoma cells was significantly associated with ER, high pathological N factor, and high Ki-67 labeling index. APP immunoreactivity was significantly positively correlated with high pathological N factor. FE65, APP and p-APP were all significantly correlated with shorter disease-free survival of breast cancer patients. In addition, FE65 status in carcinoma cells was also significantly associated with overall survival of the patients. Results of in vitro analysis revealed that FE65 promoted the cell migration and proliferation of T-47D and ZR-75-1 breast carcinoma cells. In situ proximity ligation assay also revealed that FE65 could bind to APP in the cytoplasm. FE65 status was also significantly associated with APP and ER in carcinoma cells, suggesting their cooperativity in promoting carcinoma cell proliferation and migration. In addition, APP status was significantly correlated with

adverse clinical outcome of the patients. OPN status was also associated with metastasis and poor response to tamoxifen (TAM) treatment in ER-positive breast cancer.

Conclusions

This is the first study to explore the clinical significance of FE65 in human breast cancer patients. The significant positive correlation of FE65 with poor outcome, and correlation among FE65, APP and OPN status were also firstly demonstrated in this study. In addition, FE65 or OPN knockdown promoted T-47D and ZR-75-1 sensitivity to TAM, suggesting their significance as prognostic factors and surrogate markers of TAM therapy in ER-positive breast cancer patients.