（書式１２）

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論 文 内 容 要 旨

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Abstract

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 lymph node metastasis, 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.

【所定様式⑬No.1】大学院の課程による者（課程博士）

審　査　結　果　の　要　旨

博士論文題目　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）

所属専攻・分野名　医科学 専攻 ・ 病理診断学分野

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現在本邦でも発症頻度が増加している乳癌の発症／進展危険因子は多く報告されているが、近年中枢神経系の変性疾患でその病因として検討されてきた FE65 と APP が注目されている。今回徐は多数例の乳癌標本で FE65 と APP の発現動態を免疫組織化学的に検討し、更に in vitro のレベルで proximity ligation assay, (PLA)法、 WST-8 ／ wound healing assay で その意義を総合的に検討した。 加えて FE65 とエストロゲンシグナルの関係を精査する目的で 96 個のエストロゲン関連遺伝子の発現動態を網羅的に解析した。徐の今回の検討で FE65 は乳がん患者で種々の予後不良因子と有意の相関関係を示し APP はリンパ腺転移動態と有意の関係を示した。加えて FE65, APP,そして APP の活性化型に相当する pAPP いずれも実際の乳癌患者の臨床予後と密接な相関関係が見られた。 中でも FE65 は独立した予後因子である事が判明し、PLA 法で FE65 と細胞質内の APP が直接相互作用する事も証明した。またこれらの発現動体は乳癌の内分泌療法であるタモキシフェンの治療抵抗性とも関係する事が初めて示され、今後の臨床面での応用も期待された。

よって，本論文は博士（医学）の学位論文として合格と認める。