主 論 文 要 旨

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論文題名　FXYD3 is down-regulated by TGF-β signaling and over-produced in breast cancers.

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主論文要旨

FXYD3 was originally identified as a gene product overexpressed in mouse and human breast cancers. To elucidate whether the expression of FXYD3 mRNA was regulated by TGF-β signaling, we used a normal human mammary epithelial cell line, MCF-10A which responds to TGF-β signaling, followed by induction of epithelial-to-mesenchymal transition (EMT) and growth arrest. FXYD3 localizing at plasma membrane in epithelial state of MCF-10A cells was decreased by TGF-β signaling. The repression of FXYD3 mRNA was abolished by TGF-β Receptor I inhibitor or Smad3 inhibitor. The repression of FXYD3 mRNA was also recovered by silencing of ZEB1/δEF1 transcriptional repressor which was a down-stream target gene of TGF-β. On the other hand, EMT was not induced, but cell growth retardation was observed by silencing of FXYD3 in MCF-10A and human breast cancer MCF-7 cells. These results suggested that FXYD3 was a target gene of TGF-β signaling through ZEB1/δEF1, and responsible for growth arrest, but was not directly involved in EMT in TGF-β signaling.

FXYD3 has two isoforms (FXYD3a and FXYD3b), however, there have been no reports in which these two mRNAs were separately quantified. I newly studied the expression of these isoforms separately on mRNA and protein levels, and found that FXYD3a is a major isoform of FXYD3 expressing both in human normal tissues and cancer cell lines. FXYD3 protein was overexpressed in human breast cancer specimens; invasive ductal carcinomas and intra-ductal carcinomas, whereas its expression was low in benign lesion specimens; mastopathy, fibroadenoma and phyllodes tumors. Cell proliferation rate of MCF-7 was drastically decreased by silencing of both FXYD3a and FXYD3b, but not by silencing of FXYD3b alone. These results suggested that FXYD3a protein was highly expressed in breast cancers, and responsible for proliferation of cancer cells.