東北医科薬科大学

審査学位論文（博士）要旨

氏名（本籍）	リョウ　サイシャ 梁　　彩霞（中国）
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論文審査委員	主査　　教 授　藤村　務
	副査　　教 授　山口芳樹
	副査　　教 授　顧　建国

Functional analysis of α1,6-Fucosyltransferase (FUT8) in pancreatic carcinoma cell lines

（膵がん細胞における FUT8 の機能解析）

東北医科薬科大学大学院薬学研究科

細胞制御学教室　梁　彩　霞

Pancreatic carcinoma is one of the deadliest malignant diseases, in which the increased expression of α1,6-fucosyltransferase (FUT8), a sole enzyme responsible for catalyzing core fucosylation, which catalyzes the transfer of a fucose from GDP-fucose to the innermost GlcNAc residue via α-1,6 linkage (Fig. 1), has been reported.

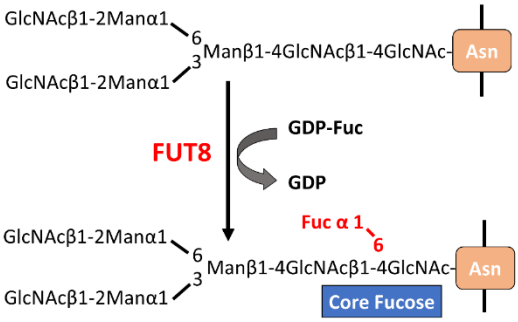

Figure 1. Reaction pathway for the synthesis of core fucose.

FUT8 play crucial roles in malignant behaviors, such as tumor growth and metastasis in several cancers. However, its pathological roles and regulatory mechanisms in pancreatic cancer remain largely unknown. Here, we use two pancreatic adenocarcinoma cell lines, MIA PaCa-2 and PANC-1 cells, as cell models, to explore the roles of FUT8. We found that a FUT8 gene knockout (FUT8-KO) using CRISPR/Cas9 inhibited cell migration when examined in transwell and wound-healing assays. In MTT and colony-formation assays the FUT8-KO significantly reduced cell proliferation. The potential inhibitory effects were also observed and verified in xenograft tumors in vivo. Moreover, the expression levels of cancer stemness markers such as EpCAM, CXCR4, c-Met, and CD133 were decreased in the FUT8-

KO cells compared with wild-type cells. Also, the spheroid formations in the KO cells were loose and unstable, which was confirmed by pipetting. Additionally, FUT8-KO increased the chemosensitivity to gemcitabine, which is the first-line therapy for advanced pancreatic cancer (Fig. 2).

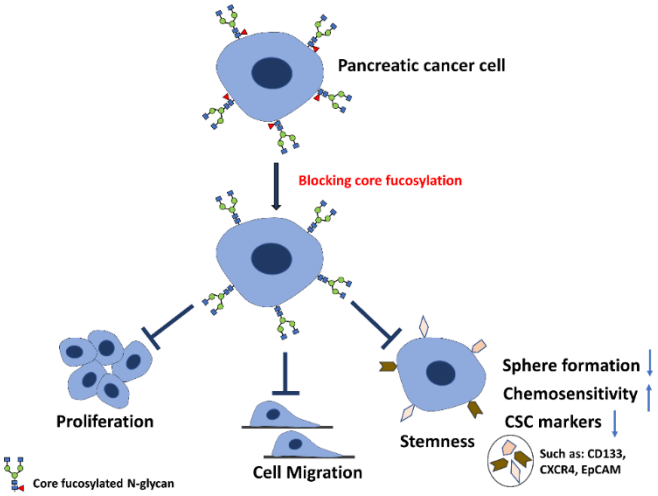

Figure 2. Schematic diagram of FUT8 in pancreatic cancer.

These novel findings are the first to suggest that the expression of FUT8 is involved in regulating the stemness features of pancreatic cancer cells. Taken together, this study clearly shows that FUT8 has important biological functions in pancreatic cancer, which could provide insights for the treatment of pancreatic carcinoma.

〈参考文献〉主論文（原著論文）

Liang C, Fukuda T, Isaji T, Duan C, Song W, Wang Y, Gu J. α1,6-Fucosyltransferase contributes to cell migration and proliferation as well as to cancer stemness features in pancreatic carcinoma. Biochim Biophys Acta Gen Subj. 2021 Jun;1865(6):129870.