



Title	Functional inactivation of oligosaccharyltransferase A isoform suppresses tumor metastasis
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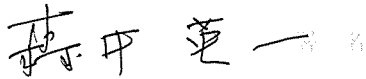
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論 文 内 容 の 要 旨
Synopsis of Thesis

氏 名 Name	SHI YANG
論文題名 Title	Functional inactivation of oligosaccharyltransferase A isoform suppresses tumor metastasis (オリゴ糖転移酵素Aアイソフォームの機能的不活化は腫瘍転移を抑制する)
論文内容の要旨 〔目 的(Objective)〕 Oligosaccharyltransferase (OST) is a multi-membrane protein complex that catalyzes the addition of glycans to Asn residues within the consensus sequences (Asn-Xaa-Ser/Thr, Xaa ≠ Pro) of nascent polypeptides in the lumen of the endoplasmic reticulum (ER). This process is termed <i>N</i>-glycosylation. In mammals, <i>N</i>-glycosylation is mediated by two distinct OST isoforms that contain either STT3A or STT3B as the catalytic subunit (OST-A and OST-B) to maximize <i>N</i>-glycosylation efficiency. Emerging evidence has demonstrated that in some cancer types, an uncompetitive OST inhibitor that targets both STT3A and STT3B has a potential to suppress cancer cell phenotypes, such as cell proliferation, treatment resistance, and secretion of small extracellular vesicles (EVs). Although these findings highlight OST as a key regulator of cancer progression, little is known about the role of individual OST isoforms in tumor progression. We aimed to elucidate the function of individual OST isoforms in tumor progression and develop ways to inhibit their functions. 〔方法ならびに成績(Methods/Results)〕 To investigate the individual roles of OST isoforms in subcutaneous tumor growth, experimental lung metastasis and EV-mediated mRNA transfer, a syngeneic mouse model with Cre-loxP system was employed. B16-F10 melanoma cells were engineered to express <i>Cre25nt</i> mRNA by retroviral transduction, enabling visualization of EV-mediated mRNA transfer from tumor cells to host cells in reporter mice by immunofluorescence (IF) staining. The <i>Stt3a</i> and <i>Stt3b</i> genes were separately knocked out (KO) in <i>Cre25nt</i>-expressing cells by using CRISPR-Cas9 system. The KO cell lines were used to generate gene-rescued counterparts. Western blot analysis showed that <i>Stt3a</i>-KO resulted in defective <i>N</i>-glycosylation of an OST-A-dependent glycoprotein (integrin β1), while <i>Stt3b</i>-KO selectively impaired <i>N</i>-glycosylation of an OST-B-dependent glycoprotein (Glut1). The defective <i>N</i>-glycosylation in <i>Stt3a</i>-KO and <i>Stt3b</i>-KO cells was restored upon their gene rescue. Subcutaneous tumor model revealed that KO of <i>Stt3a</i> or <i>Stt3b</i> did not compromise tumor growth, immune and endothelial cell infiltration, EV-mediated mRNA transfer, and invasive margin between tumor and surrounding tissues. In contrast, lung colonization assay revealed that co-expression of <i>Stt3a</i> and <i>Stt3b</i> was critical for lung colonization. Our study further revealed that the cytosolic N-terminal region of Stt3a was critical for OST-A-dependent <i>N</i>-glycosylation and lung colonization. 〔総 括(Conclusion)〕 In summary, we discovered the functional role of the individual OST isoforms in melanoma progression and identified the cytosolic N-terminal region of Stt3a as a key regulatory region of OST-A and tumor metastasis. This study opens a novel avenue for selective manipulation of OST-A activity, which might offer potential therapeutic strategies for metastatic cancers.	

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨 Oligosaccharyltransferase (OST)は、小胞体内でasparagine-linked glycosylation (N-glycosylation)を触媒する酵素である。哺乳類では2個の異なるisoformであるOST-A, OST-Bが存在する。今回はこの2個のisoformの機能的差異を検討した。マウスメラノーマの転移モデルにおいて、OST-A, OST-Bの両者が存在しないと転移が成立しないこと、OST-Aの触媒部位であるN末端に存在するStt3a regionが転移に重要な役割を示すことを示した。2個のisoformがあるが、このうちOST-Aを制御することで、転移の抑制を行うことが今回の研究では示された。腫瘍の転移を抑制するための薬剤開発では、このOST-AのN末端に存在するStt3a regionをターゲットにすればいいことが示唆される。本研究は転移メカニズムに迫るものであり、薬剤開発ターゲットの同定にもつながることから、博士(医学)の学位授与に値する。				