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論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	Quan Lili　（全　麗麗）
論文題名 Title	Amino acid transporter LAT1 in tumor-associated vascular endothelium promotes angiogenesis by regulating cell proliferation and VEGF-A-dependent mTORC1 activation (腫瘍血管内皮に発現するアミノ酸トランスポーターLAT1は細胞増殖と血管新生促進因子VEGF-Aによるm TORC1活性化の制御を介して血管新生を促進する)

論文内容の要旨

〔目　的(Purpose)〕

Tumor angiogenesis is regarded as a rational anti-cancer target. The efficacy and indications of anti-angiogenic therapies in clinical practice, however, are relatively limited. Therefore, there still exists a demand for revealing the distinct characteristics of tumor endothelium that is crucial for the pathological angiogenesis. L-type amino acid transporter 1 (LAT1) is well known to be highly and broadly upregulated in tumor cells to support their growth and proliferation. In this study, we aimed to establish the upregulation of LAT1 as a novel general characteristic of tumor-associated endothelial cells as well, and to explore the functional relevance in tumor angiogenesis.

〔方法ならびに成績(Methods/Results)〕

Expression of LAT1 in tumor-associated endothelial cells was immunohistologically investigated in human pancreatic ductal adenocarcinoma (PDA) and xenograft- and syngeneic mouse tumor models. The effects of pharmacological and genetic ablation of endothelial LAT1 were examined in aortic ring assay, matrigel plug assay, and mouse tumor models. The effects of LAT1 inhibitors and gene knockdown on cell proliferation, regulation of translation, as well as on the VEGF-A-dependent angiogenic processes and intracellular signaling were investigated in in vitro by using human umbilical vein endothelial cells.

LAT1 was highly expressed in vascular endothelial cells of human PDA but not in normal pancreas. Similarly, high endothelial LAT1 expression was observed in mouse tumor models. The angiogenesis in ex/in vivo assays was suppressed by abrogating the function or expression of LAT1. Tumor growth in mice was significantly impaired through the inhibition of angiogenesis by targeting endothelial LAT1. LAT1-mediated amino acid transport was fundamental to support endothelial cell proliferation and translation initiation in vitro. Furthermore, LAT1 was required for the VEGF-A-dependent migration, invasion, tube formation, and activation of mTORC1, suggesting a novel cross-talk between pro-angiogenic signaling and nutrient-sensing in endothelial cells.

〔総　括(Conclusion)〕

These results demonstrate that the endothelial LAT1 is a novel key player in tumor angiogenesis, which regulates proliferation, translation, and pro-angiogenic VEGF-A signaling. This study furthermore indicates a new insight into the dual functioning of LAT1 in tumor progression both in tumor cells and stromal endothelium. Therapeutic inhibition of LAT1 may offer an ideal option to potentiate anti-angiogenic therapies.

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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

抗血管新生療法は合理的な悪性腫瘍治療法であるが、その有効性と適応は未だに限定的である。そのため、病態特異的な血管新生の分子機構解明と、新たな治療戦略の提唱が求められている。本研究は、腫瘍組織に広く高発現するアミノ酸トランスポーターLAT1(SLC7A5)が、これまで知られていた腫瘍細胞のみならず血管内皮細胞にも高発現することを見出した。また、血管内皮細胞のLAT1を標的として腫瘍血管新生の抑制による抗腫瘍効果が得られることを示した。その分子基盤として、LAT1によるアミノ酸輸送が血管内皮細胞の増殖に必須であることに加えて、血管新生促進因子VEGF-A下流のシグナル経路と、LAT1下流の栄養シグナル経路のクロストークの存在を明らかにした。本研究は、LAT1を抗血管新生療法の新たな標的候補として位置付け、その選択的阻害薬を用いて腫瘍細胞と血管内皮細胞を標的とした顕著な抗腫瘍効果が得られることを示したものであり、学位に値するものと認める。