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Title	Adenylosuccinate lyase enhances aggressiveness of endometrial cancer by increasing killer cell lectin-like receptor C3 expression by fumarate
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Citation	大阪大学, 2018, 博士論文
Version Type	
URL	https://hdl.handle.net/11094/69385
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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

プリン体合成酵素であるAdenylosuccinate lyase (ADSL)はこれまで大腸癌や乳癌、前立腺癌で発現が上昇していることが報告されていたが、腫瘍の悪性度にどのように寄与しているかは明らかではなかった。本論文は、子宮内膜癌における ADSL の役割を明らかにしている。具体的には、免疫組織化学染色でADSLの発現が子宮内膜癌の分化度が低下するに従い上昇し、また腫瘍のT gradeと相関することを見出した。実際にADSLが腫瘍の悪性度に寄与し得るかに関して、子宮内膜癌細胞株を用いてADSLのノックダウンを行い、増殖能、移動能、浸潤能の低下が起こることを示し、それはkiller cell lectin-like receptor subfamily C, member 3 (KLRC3)の発現低下を介することを示した。さらに、ADSLが産生しうるフマル酸によってKLRC3の発現が上昇することを示している。これら結果は、ADSLが子宮内膜癌の悪性度に寄与していること、またADSL, KLRC3が子宮内膜癌の新たな治療標的になり得ることを示しており、学位論文に値すると考えられる。

論　文　内　容　の　要　旨

Synopsis of Thesis

氏　名 Name	Park Haengki 朴　幸基
論文題名 Title	Adenylosuccinate lyase enhances aggressiveness of endometrial cancer by increasing killer cell lectin-like receptor C3 expression by fumarate (Adenylosuccinate lyase は フマル酸による killer cell lectin-like receptor C3 の発現上昇を介して子宮内膜癌の悪性度を増強する)

論文内容の要旨

〔目　的(Purpose)〕

The purpose of this study is to elucidate the role of ADSL in endometrial cancer.

〔方法ならびに成績(Methods/Results)〕

Methods:

First, we examined ADSL expression in clinical specimens from 100 cases of endometrioid carcinoma by immunohistochemistry. Then, we conducted in vitro functional assays of siRNA-mediated knockdown of adenylosuccinate lyase (ADSL) using the endometrial cancer cell lines HEC1B, HEC108 and SNGM. We performed DNA microarray-based gene expression profiling using ADSL knockdown and control HEC1B cells. Thereafter, we conducted in vitro functional assays of siRNA-mediated knockdown of killer cell lectin-like receptor C3 (KLRC3) using the endometrial cancer cell lines HEC1B, HEC108 and SNGM. We examined KLRC3 mRNA expression by quantitative real time PCR and conducted in vitro functional assay after adding fumarate to cells transfected with siADSL.

Result:

The expression levels of ADSL increased as endometrioid carcinoma specimens became more poorly differentiated. And also, the expression levels of ADSL were higher in the cases of high degree of primary tumor progression, T2 and T3 than in the ones of T1. The positivity of ADSL expression was not correlated with the degree of lymph node metastasis. In vitro functional assay of HEC1B, HEC108 and SNGM cells, knockdown of ADSL resulted in decreased cell proliferation, migration and invasion capability. And also, knockdown of ADSL reduced Akt phosphorylation. In DNA microarray-based gene expression profiling, among the top 25 molecules, we identified KLRC3, which has been described as a receptor on natural killer cells and was recently shown to be involved in glioblastoma tumorigenesis and aggressiveness. KLRC3 knockdown in HEC1B, HEC108 and SNGM cells induces the same phenotypes as ADSL knockdown, that is, reduced cell proliferation and migration capability. ADSL knockdown cells treated with diethyl fumarate, which could be produced by ADSL, recovered expression of KLRC3 in HEC1B, HEC108 and SNGM cells. Furthermore, Treatment with diethyl fumarate restored cell migration capability reduced by ADSL knockdown.

〔総　括(Conclusion)〕

We have demonstrated that ADSL is involved in tumor cell proliferation, migration, invasive capability, and cell shape reorganization via regulation of KLRC3 expression by fumarate possibly produced by ADSL in endometrial cancer. These findings provide novel evidence for the contributions of ADSL and KLRC3 to tumor cell aggressiveness. Thus, ADSL and KLRC3 are potential new targets for the development of novel therapies for endometrial cancer.