学位の種類	博士（医学）
報告番号	甲第１６６１号
学位記番号	第１１８１号
氏名	竹下　奨
授与年月日	平成 30 年 8 月 31 日
学位論文の題名	Expression of P-REX2a is associated with poor prognosis in endometrial malignancies (P-REX2a の発現は子宮体癌において予後不良因子である) Oncotarget 2018; 37: 24778-24786
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Abstract

Phosphatidylinositol-3,4,5-trisphosphate RAC exchanger 2a (P-REX2a) is a member of the P-REX protein family which are activated by phosphatidylinositol-3,4,5-trisphosphate that act as Rho/Rac guanine nucleotide exchange factors. P-REX2 was at first found to activate the small GTPase Rac, downstream of G protein-coupled receptors and phosphoinositide 3-kinase (PI3K) to enhance cell motility. Later, a new role of P-REX2a had been identified to inhibit the lipid phosphatase activity of PTEN to stimulate the PI3K pathway and enhance cell viability, movement and growth. No associations with P-REX2a and human endometrial cancers have been reported to date. In this study, we immunohistochemically analyzed 155 uterine endometrial malignancies for P-REX2a expression. The P-REX2a-positive tumors displayed worse prognosis independent of PTEN expression. Then, we transduced either P-REX2a expression vector or short hairpin RNAs targeting P-REX2a into 2 uterine endometrioid carcinoma cell lines, OMC-2 and JHUEM-14. Ectopic expression of P-REX2a led to increased cell proliferation only in the PTEN-expressing OMC-2 cells but did not show any change in the PTEN-negative JHUEM-14 cells or the P-REX2a-knockdown cells. Induction of P-REX2a increased and knockdown of P-REX2a decreased cell migration in both cell lines. Then, we performed expression microarray analysis using these cells, and pathway analysis revealed that the

expression of members of the GPCR downstream pathway displayed the most significant changes induced by the knockdown of P-REX2a. Immunohistochemical analysis revealed that Vav1, a member of the GPCR downstream pathway, was expressed in 139 of the 155 endometrial tumors, and the expression levels of Vav1 and P-REX2a showed a positive correlation ($r=0.44$, $p<0.001$). In conclusion, P-REX2a enhanced cell motility via the GPCR downstream pathway independently of PTEN leading to progression of uterine endometrioid malignancies and poor prognosis of the patients.