学位論文要約
Extended Summary in Lieu of the Full Text of a Doctoral Thesis

氏　　名：
Full Name　Motoki Takenaka

学位論文題目：　Iron regulatory protein 2 in ovarian endometrial cysts.
Thesis Title

学位論文要約：
Summary of Thesis

Ovarian endometrial cysts cause some kinds of ovarian cancer, and iron is considered as one factor of carcinogenesis. In contrast, hypoxia is associated with progression, angiogenesis, metastasis, and resistance to therapy in cancer. We investigated hypoxia-induced perturbation of iron homeostasis in terms of labile iron, iron deposition, and iron regulatory protein (IRP) in ovarian endometrial cysts. Iron deposition, expression of IRPs, and a protein marker of hypoxia in human ovarian endometrial cysts were analyzed histologically. The concentration of free iron and the pO2 level of the cyst fluid of human ovarian cysts (n = 9) were measured. The expression of IRP2 under hypoxia was investigated in vitro by using Ishikawa cells as a model of endometrial cells. Iron deposition and the expression of IRP2 and Carbonic anhydrase 9 (CA9) were strong in endometrial stromal cells in the human ovarian endometrial cysts. The average concentration of free iron in the cyst fluid was 8.1 ± 2.9 mg/L, and the pO2 was 22.4 ± 5.2 mmHg. A cell-based study using Ishikawa cells revealed that IRP2 expression was decreased by an overload of Fe(II) under normoxia but remained unchanged under hypoxia even in the presence of excess Fe(II). An increase in the expression of IRP2 caused upregulation of intracellular iron as a result of the response to iron deficiency, whereas the protein was degraded under iron-rich conditions. We found that iron-rich regions existed in ovarian endometrial cysts concomitantly with the high level of IRP2 expression, which should generally be decomposed upon an overload of iron. We revealed that an insufficient level of oxygen in the cysts is the main factor for the unusual stabilization of IRP2 against iron-mediated degradation, which provides aberrant uptake of iron in ovarian endometrial stromal cells and can potentially lead to carcinogenesis.