学 位 論 文 の 要 旨

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学 位 論 文 名　Difference in P57 Expression Among Four Histological Types of Epithelial Ovarian Carcinoma.

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論 文 内 容 の 要 旨

INTRODUCTION

The cyclin-dependent kinase inhibitor, P57, negatively regulates cell division cycle and keeps cells at the G0 period. P57 was reported to be expressed at a low level in some malignant tumors and was suggested to play an important role as a tumor suppressor since expression of P57 inversely correlated with the histological grade and/or the clinical stage of carcinomas.

Several reports showed that P57 was expressed in epithelial ovarian carcinoma (EOC) as well. However, the correlation of the EOC histology with P57 expression was not yet elucidated despite that the histology was an important prognostic factor for EOC.

EOC has four major histological subtypes; endometrioid carcinoma (EC), serous carcinoma (SC), mucinous carcinoma (MC) and clear cell carcinoma (CCC). In this study, we performed an immunohistochemical analysis of P57 in 92 EOC cases to examine the potential usefulness of P57 in the differential diagnosis of EOC.

MATERIALS AND METHODS

We collected histological samples of 92 EOC cases surgically resected either at Shimane University Hospital, Hamada Medical Center or Matsue Red Cross Hospital

between January 2011 and July 2016. In 92 cases, there were 31 high-grade SCs (HGSCs), 29 CCCs, 18 ECs and 14 MCs. As we had only two cases of the low-grade SC, we used only HGSCs in the present study. Patients' age, clinical stage and histological grade were obtained from medical records. Histological grade of CCC was not determined according to the standardized diagnostic protocol. We applied an opt-out policy under the permission of the ethical committee of Shimane University. The study protocol was approved by the Research Ethics Committee of Shimane University Faculty of Medicine (#20161130-1), of Hamada Medical Center (#2817), and of Matsue Red Cross Hospital (#320).

The pathological slides were incubated with a mouse monoclonal anti-P57 (1:200, sNCL-p57, clone 25B2, Nicastro/Leica, Nassloch, Germany), followed by incubation with a secondary antibody (EnVision, DAKO/Agilent, Santa Clara, CA). Staining was done with diaminobenzene by avidin-biotin peroxidase complex method. Cases were interpreted as 'nuclear and cytoplasmic P57-positive' when more than 5% of tumor cells showed clear brown-yellow granules in the nucleus and the cytoplasm, respectively.

The associations between P57 expression and all variables were assessed using the contingency table analysis, Fisher's exact test and logistic regression analysis. $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

We identified 5 positive cases out of 29 cases of CCC, which was significantly greater than in non-CCC (17.2 and 1.6% for CCC and non-CCC, respectively, p=0.01 by Fisher's exact test). In contrast, for cytoplasmic P57, a greater prevalence of positive cases was obtained in EC than in non-EC (55.6 and 23.0% for EC and non-EC, respectively, p=0.01 by Fisher's exact test). The logistic regression analysis confirmed the effects of the histology on nuclear and cytoplasmic P57 expression under adjustment with patients' age and the clinical stage.

In this study using 92 cases of EOC, we found that cases with nuclear P57 expression were more prevalent in CCC while cases with cytoplasmic P57 expression were more prevalent in EC. This result was interesting if biological characteristics of EOC as well as regulatory roles of P57 in cell proliferation were considered. Despite such interesting features of P57 expression, P57 did not seem a reliable marker in the histological diagnosis of EOC because less than 30% of tumor cells were positive even at a maximum.

P57 is, like P21 and P27, a cyclin-dependent kinase inhibitor, which becomes active after translocation into the nucleus. It was therefore generally accepted that a lower level of P57 expression in the nucleus was an indicator of a poor prognosis in various cancers. In contrast to nuclear P57 expression, cases positive for cytoplasmic P57 expression were significantly greater in EC than in other histological types. These observations suggested that the difference in intracellular P57 expression might reflect biological or pathogenetic feature of EOC; cytoplasmic expression of P57 was implicated to affect various functions in cancer cells such as motility of cells, stabilization of the actin cytoskeleton, inhibition of apoptosis, and suppression of invasion and metastasis. Although the present study failed to support the relationship between P57 expression and clinical stage of EOC, further cell biological studies are warranted to clarify roles of cytoplasmic P57 in biological behavior of EOC.

CONCLUSION

We examined P57 expression in 92 cases of EOC including 4 different histological types, and found that nuclear and cytoplasmic P57 expression was greater in CCC and EC, when compared with non-CCC and non-EC, respectively. This observation would be useful to clarify difference in biological features of four histological types of EOC.