GROWTH REGULATION OF EPITHELIAL OVARIAN CANCER CELL LINES
BY FEMALE SEX HORMONES.

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Background Over 95% of patients who have been treated for ovarian cancer will experience menopause, whether it be natural or treatment-related. Therefore, the use of female hormone replacement therapy has become inevitable for epithelial ovarian cancer patients, but differing opinions on its use still exist, even now. So the effects of low dose of estradiol as a respect of hormone replacement therapy on the proliferation of epithelial ovarian cancer are investigated through in vitro and in vivo.

Methods In vitro, the six epithelial ovarian cancer cell lines containing different estrogen receptors were used : OVCAR-3, MDAH2774, PA-1, SNU-8, and ES-2 for XTT. The difference in the proliferation was compared between the group treated with FSH and LH (FL group), the group with FSH, LH and additionally estradiol (FLE group). Using flow cytometry, the changes in the cell cycle of the epithelial ovarian cancer cell lines between the FL group and FLE group were analyzed. In vivo, OVCAR-3 was xenografted in female NOD-SCID mice, which had both ovaries removed, to compare the extent of proliferation of the xenograft tumor between the FL group and FLE group. And then the difference in proliferation was confirmed in the xenograft tumor tissues through the immunohistochemical staining for PCNA and p53. Moreover, it was examined that the expressions of the proteins-Rb, p16, cyclin D1, which controls cell cycle progression from G1 to S phase by Western to investigate the mechanism behind the arrest at the G0/G1 phase.

Results In vitro, the difference of proliferation in FLE group compared to the FL group was not statistically significant ($P > 0.05$). In flow cytometric assay, FL group tended to distribute the cell cycle to the S phase, compared to the control group, and the addition of estradiol tended to arrest the cell cycle at the G0/G1 phase, compared to FL group. In vivo, the proliferation of xenograft tumor was suppressed in FLE group, compared to the FL group ($P < 0.05$). In the immunohistochemical staining for PCNA, it was more frequently and strongly expressed in FL group than FLE group. But for p53, it was so weakly expressed that it can not be compared. In addition, the expression of Rb protein was stronger in FLE group than in FL group. On the other hand cyclin D1 expression was significantly evident in FL group, while the expression of p16 was very weak so that it could not be compared.

Conclusion The results of this study show that estradiol does not promote the proliferation of epithelial ovarian cancer but rather decrease the proliferation that was promoted by FSH and LH during menopause ; this may due to the arrest of cell cycle at G0/G1 phase by estradiol.