学 位 論 文 の 要 旨

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学 位 論 文 名	Mucinous Borderline Ovarian Tumors With *BRAF*^{V600E} Mutation May Have Low Risk for Progression to Invasive Carcinomas
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論 文 内 容 の 要 旨

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy worldwide. Mucinous ovarian carcinoma proposed to develop in a stepwise manner from a benign cystadenoma to a borderline tumor, and then to a carcinoma. Mucinous ovarian carcinoma (MOC) has a good prognosis if diagnosed at an early stage; however, its prognosis is poor at advanced stages as it tends to be chemoresistant, particularly to platinum drugs.

The RAS-RAF-MEK-ERK-MAP kinase pathway is often implicated in carcinogenesis; particularly, RAS oncogenes are key factors in tumor development. *BRAF* and *KRAS* mutations are components of the mitogen-activated protein kinase (MAPK) cascade and *KRAS* mutations are common in mucinous ovarian tumors and prevalent among 40–50% of MOC cases and it may play a major role in the progression from benign tumors to carcinomas.

BRAF mutations brings about ERK activation and were reported in a large proportion of cases of malignant melanoma with poor outcomes. In contrast, they were reportedly associated with early-stage disease and improved outcomes in patients with low-grade serous ovarian cancer. Thus far, the role of *BRAF* mutations in mucinous ovarian carcinogenesis remains unclear. In the present study, we retrospectively investigated the mutation patterns of *BRAF, KRAS*, *PIK3CA*, and *TP53* in mucinous cystadenomas (MCAs), mucinous borderline tumors (MBTs), and MOC to clarify the role of each gene in mucinous ovarian carcinogenesis.

MATERIALS AND METHODS

Formalin-fixed, paraffin-embedded tissue samples of 16 MOC, 10 MBT, and 12 MCA patients were used in this study. All patients were primarily treated via surgery (i.e., total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy) with or without pelvic and para-aortic lymph node dissection and adjuvant taxane/platinum combination chemotherapy.

Sixteen MOC, 10 MBT, and 12 MCA cases had sufficient tumor tissue for DNA extraction and sequence analysis. After 48 hours of digestion with a proteinase, DNA was extracted from the microdissected samples.

Polymerase chain reaction amplification was performed on exon 2 of *KRAS*, exon 15 of *BRAF*, exons 4 to 9 of *TP53*, and exons 9 and 20 of *PIK3CA*, using genomic DNA obtained from microdissected formalin-fixed, paraffin-embedded tissue.

All results are expressed as means ± standard deviations. In some cases, the three groups were compared using the chi-square test and the Tukey-Kramer test, as appropriate. All differences in analysis items were considered significant at $p<0.05$.

This study protocol was approved by the Ethics Committee of Shimane University (approval no. 2004-0381) and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

All 38 cases were assessed for mutations in the *KRAS*, *BRAF*, *TP53*, and *PIK3CA* genes. *KRAS* mutations were detected in 7 of the 16 (43.8%) MOC cases and in 2 of the 10 (20%) MBT cases. However, no *KRAS* mutations were detected in MCA cases. *KRAS* mutations tended to occur more frequently in MBT than in MCA (p=0.066, chi-square test). *BRAF* mutations in exon 15 were only detected in 4 of the MBT cases, but not in the MOC or MCA cases. None of the mucinous tumor specimens showed *TP53* mutations. *BRAF* mutations occurred significantly more frequently in MBT cases than in MOC cases (*p=0.042, chi-square test). *PIK3CA* mutation was detected in only one case of MCA.

The V600E *BRAF* mutation constitutes over 90% of all *BRAF* mutations in melanoma and might be an acquired event in early invasive melanoma that induces clonal expansion and tumor progression. Consequently, *BRAF* mutation is associated with poor prognosis in not only melanoma but also papillary thyroid cancer and metastatic colon cancer. In contrast, *BRAF* mutations were present in MBT but not in MOC in this study, suggesting that *BRAF* mutations are associated with the indolent type of MBT. It has reported that the presence of *BRAF* mutations in serous borderline ovarian tumor or low-grade serous ovarian carcinoma was relevant to early-stage disease and favorable prognoses. It has been reported that lack of *Cdkn2a* in V600E *BRAF* mutated melanocytes in rodents is associated with rare progression to melanoma.

In MOC, *Cdkn2a/b* homozygous deletions/mutations were detected at high frequencies. From these reports, it appears that loss of *Cdkn2a* in mucinous ovarian tumors with V600E *BRAF* mutation impairs progression to carcinoma. Therefore, BRAF mutation is associated with early-stage disease, such as MBT, and was not detected in MOC in the present study.

KRAS is the predominant mutated gene in MOC and may be related to the progression from benign to malignant tumors. Our results are consistent with those of previous studies regarding *KRAS*, the prevalences of *KRAS* mutations were 0%, 20%, and 43% among MCA, MBT, and MOC specimens, respectively. We also found that some cases had both *KRAS* and *BRAF* mutations in MBT. These MBT cases with both *KRAS* and *BRAF* mutations might progress to MOC earlier than would those without these mutations.

CONCLUSION

V600E *BRAF* mutations were detected only in MBT, while G12D/G13D *KRAS* mutations were detected more commonly in MOC than in MBT. We posit that MBT with V600E *BRAF* mutation may not progress to MOC and predict a favorable outcome, while MBT with G12D/G13D *KRAS* mutation may progress to MOC in the future.