学 位 論 文 の 要 旨

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学 位 論 文 名　High Frequency of *PIK3CA* Mutations in Low-Grade Serous Ovarian Carcinomas of Japanese Patients

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論 文 内 容 の 要 旨

INTRODUCTION

Ovarian cancer is the leading cause of death owing to gynecologic malignancies in the world. Recently, ovarian cancer was subdivided into two categories, Type I and Type II. Type II tumors mainly include high-grade serous carcinomas (HGSCs) with *TP53* mutations and show an aggressive clinical course. In contrast, Type I tumors include low-grade serous carcinomas (LGSCs), mucinous carcinomas, and clear cell carcinomas. LGSCs are more common in younger patients and associated with chemoresistance than HGSCs. Previous reports from Western countries have indicated that LGSCs have a higher frequency of *KRAS* (16–54%) or *BRAF* (2–33%) mutations. Therefore, KRAS/BRAF/ERK signaling pathways are thought to be essential in the carcinogenesis of LGSC in Europe.

However, the frequency of *KRAS/BRAF* mutations associated with low-grade serous ovarian carcinoma (LGSC)/serous borderline tumors (SBTs) in Japan is unknown. We aimed to identify genetic variations in *KRAS, BRAF, PIK3CA*, and *ERBB2* in LGSC/SBT/serous cystadenomas (SCAs) in a Japanese population.

MATERIALS AND METHODS

Formalin-fixed paraffin-embedded tissue samples from 10 LGSC, 17 SBT, and 12 SCA patients were analyzed in this study. The samples were retrieved from the Department of

Obstetrics and Gynecology, Shimane University Hospital (Izumo, Japan), Seirei Hamamatsu General Hospital, and Shimane Prefectural Central Hospital from 2007 to 2017. Ten LGSC, 11 SBT, and 12 SCA cases had sufficient tumor tissue for DNA extraction and sequence analysis. Sanger sequencing was performed on polymerase chain reaction (PCR)-amplified *KRAS*, *BRAF*, *PIK3CA*, and *ERBB2* using genomic DNA obtained from microdissected formalin-fixed paraffin-embedded tissue. Immunohistochemistry of p53 and ARID1A was also performed. Loss of ARID1A expression in tumor cell nuclei was used as a surrogate for the presence of ARID1A loss-of-function mutations. Similarly, p53 immunoreactivity was used as a surrogate for the presence of p53 loss-of-function mutations. This human subjects research was approved by the Ethics Committee of the Shimane University Hospital (approval no. 2004-0381), and written informed consent was obtained from all patients.

RESULTS AND DISCUSSION

The frequency of oncogenic mutations in *PIK3CA* was 60.0% (6/10) in LGSCs, 63.6% (7/11) in SBTs, and 8.3% (1/12) in SCAs. All cases harbored wild-type *KRAS*. The frequency of *BRAF* mutations was 20.0% (2/10) in LGSCs, whereas all SBTs and SCAs harbored the wild-type allele. The frequency of *ERBB2* mutations was 30.0% (3/10) in LGSCs, 0.0% (0/11) in SBTs, and 16.7% (2/12) in SCAs. ARID1A staining was positive in all cases. p53 staining was positive in 0% (0/10) LGSCs, 9.1% (1/11) SBTs, and 0.0% (0/12) SCAs. One LGSC case had two *PIK3CA* mutations (G1633A and G3149A) in both LGSC and SBT lesions, but a *BRAF* mutation was detected only in an LGSC lesion.

These results suggest that, compared with the values in Western populations (16–54%), the *KRAS* mutation frequency in LGSCs/SBTs is lower and that of *PIK3CA* mutations in LGSCs/SBTs is much higher in Japanese populations. Therefore, the main carcinogenesis signaling pathways may be different between Japanese and Western LGSCs. In the current study, wild-type *KRAS* was found in all Japanese LGSC, SBT, and SCA cases. In contrast, *BRAF* mutations were detected in 20% (2/10) of LGSCs.

These findings suggest that genes driving LGSC may be different in Asian and Western populations. Furthermore, the prevalence of oncogenic mutations in *PIK3CA* in both LGSCs and SBTs was much higher in Japanese patients than in Western patients. This high prevalence of oncogenic *PIK3CA* mutations in both SBTs and LGSCs suggests that these mutation events occur early in LGSC carcinogenesis. The incidence of LGSC is quite low in Japan; therefore, a large multi-institutional cohort study is needed to confirm the current findings.

The current study has several limitations. First, the number of samples in this study was small. A follow-up study with an increased number of subjects is ongoing. This will enable us to determine, statistically, the relationship between the mutations identified in the present study and patient outcomes. Second, we identified genetic mutations via Sanger sequencing; therefore, the kinds of gene mutations assessed were limited. Further analyses using next-generation sequencing will also be needed to determine the molecular mechanism that underlies progression

to LGSC in Japanese patients.

CONCLUSION

Based on the current findings, we hypothesize that the main oncogenic signaling pathway in Japanese LGSCs is PIK3CA/AKT, whereas that in Western LGSCs is KRAS/BRAF/ERK. The current findings suggest that the mutation frequency of *KRAS* in LGSCs/SBTs in Japan is lower than that in Western countries. In addition, the mutation frequency of *PIK3CA* in LGSCs/SBTs appears to be very high in a Japanese population compared to Western populations. *PIK3CA* mutation may be a main driver and *BRAF* or *ERBB2* mutation may be a sub-driver event in Japanese LGSCs. Therefore, molecular therapies targeting the PIK3CA/AKT pathway may be effective in LGSCs in Japan.