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Molecular-Biological Characteristics of Type I, Ovarian Low-Grade Serous and Mucinous Carcinomas and Prospects of Molecular-Targeted Therapy

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Abstract

Two models of carcinogenesis have recently been proposed for ovarian cancer based on the differences in the mechanism of carcinogenesis. Low-grade serous carcinoma and mucinous carcinoma are classified as type I, and high-grade serous carcinoma and high-grade endometrioid carcinoma are classified as type II ovarian cancers.

Low-and high-grade serous carcinomas were reported to have independent pathologies based on their morphological characteristics, molecular mechanism of histogenesis, and clinical features. Serial activation of the components of the mitogen activated protein kinase (MAPK) signaling pathway was observed in low-grade serous carcinomas resistant to existing anticancer drugs, and the efficacy of MEK inhibitors targeting these signals has been demonstrated. The morphology- and molecular biology-based elucidation of the pathology of ovarian cancers might lead to the implementation of personalized treatment through molecular-targeted therapy.

Keywords: Low-grade serous carcinoma; Mucinous carcinoma; Ovarian cancer

Introduction

Kurman and Shih et al. of Johns Hopkins University, USA, recently proposed a new classification for ovarian cancers based on their morphological characteristics, the presence of precancerous lesions, and molecular-biological characteristics of the tumor [1,2]. Low-grade serous and mucinous carcinomas are classified as type I, and high-grade serous and endometrioid carcinomas are classified as type II ovarian cancers (Figure 1).

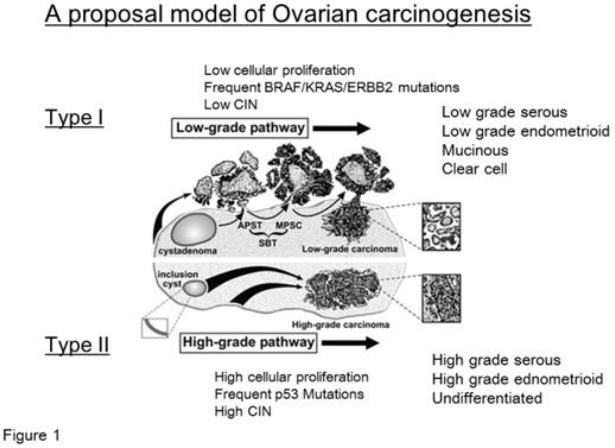

Figure 1

Figure 1: Carcinogenesis model of ovarian cancer. (Figure adapted from [1]).

Type I ovarian cancers have been reported to progress from benign to borderline malignant tumors and gradually to infiltrating cancers. *KRAS* or *BRAF* are mutated in 65% of low-grade serous carcinoma cases [3]. In contrast, in mucinous carcinomas, the frequency of *KRAS* mutations is high whereas that of *BRAF* mutations is low, and *HER2* amplification is present in approximately 30% of mucinous carcinoma cases [4]. In this report, the clinical and molecular-biological characteristics of low-grade serous and mucinous carcinomas are described and the future prospects for molecular-targeted therapy are outlined.

Clinical Characteristics of Low-Grade Serous Carcinoma

The onset age for low-grade serous carcinoma is younger than that for high-grade serous carcinoma, showing a high incidence rate in the early 40s [5]. The ratio of low- to high-grade serous carcinoma cases among all serous carcinoma cases is 1:9, indicating a very low incidence of low-grade serous carcinoma [6]. Anticancer drug sensitivity of low-grade serous carcinoma is lower than that of high-grade serous carcinoma [5]; however, the clinical prognosis is more favorable than that of high-grade serous carcinoma [7]. These findings might reflect the biological characteristics of the disease, which is a tumor of low malignant potential. The indications for secondary cytoreductive surgery (SDS) for recurrence are the presence of a solitary lesion or 2 lesions and the possibility of complete removal by surgery. SDS might be indicated for many cases of low-grade serous carcinoma because disease progression is slow and it is resistant to existing chemotherapy regimens [8]. Recently, Gershenson et al. [5] reported that woman aged <35 years with low-grade serous carcinoma and those with persistent disease at the end of therapy have the worst outcomes [9].

Molecular-Biological Characteristics of Low-Grade Serous Carcinoma

Low-grade serous carcinoma is accompanied by a serous borderline tumor as a precancerous lesion, and carcinogenesis is considered to occur through the adenoma-carcinoma sequence [1]. In high-grade serous carcinoma, the *p53* gene mutation is noted at a frequency of almost 100% [10], whereas this mutation is absent in low-grade serous carcinoma [3]. It was reported that in low-grade serous carcinoma, somatic cell mutation of *KRAS*/*BRAF* (oncogenic mutation) is present in a mutually exclusive manner; abnormality is present in one of these genes at approximately 65% frequency, and the downstream MAPK signal is constitutively activated [11]. We previously reported that a 12 base-pair insertion mutation of *HER2* (ERBB2) occurred in low-grade serous carcinoma without *KRAS*/*BRAF* mutation at a frequency of 9% [3]. We also discovered that the *KRAS/BRAF* mutation might serve as a biomarker for the efficacy of MEK1/2 inhibitors [12]. In order to investigate the presence of a new oncogene, we performed exome sequencing of low-grade serous carcinoma [13]; however, no new oncogene other than the *KRAS*/*BRAF* oncogene with mutation was detected [13]. We previously reported a low frequency for gene copy number mutations in low-grade serous carcinoma [14]. We considered the involvement of abnormal microRNAs and the epigenome in carcinoma is (Figure 2).

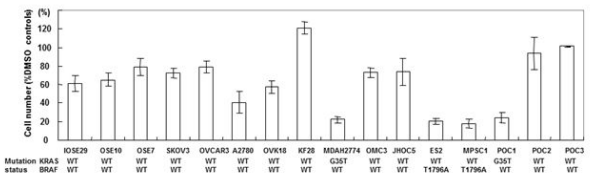

Figure 2: KRAS/BRAF gene mutation in the ovarian cancer cell line and the effect of the MEK inhibitor. (Figure adapted from [13]).

The results of exome sequencing of serous borderline tumors were recently reported. In addition to the previously reported oncogenic mutations of *BRAF*, *FBXW7*, and *KIAA1462*, novel gene mutations were reported [15]. Research groups from Johns Hopkins University and MD Anderson Cancer Center recently reported 2 new lines of evidence supporting the type I carcinogenesis pathway. Peritoneal implants of serous borderline tumors/atypical proliferative serous tumors, which are considered to be precancerous lesions of low-grade serous carcinoma, had the same *KRAS*/*BRAF* mutation pattern as that of the primary lesions, suggesting that these are metastatic lesions arising from the primary lesion [16]. In addition, *KRAS* mutation, but not *BRAF* mutation, was involved in the progression of a serous borderline tumor to low-grade serous carcinoma, and *KRAS G12V* mutation indicated poor prognosis [17]. Recently, Emmanuel et al. reported *NRAS* mutations in 9% of invasive serous carcinomas with adjacent serous borderline tumors suggesting *NRAS* as an oncogenic driver in low-grade serous carcinomas [18]. Furthermore, Gershenson et al. [5] reported that patients with *KRAS* or *BRAF* mutations had significantly better overall survival than those with wild type *KRAS* or *BRAF* [19].

Clinical Characteristics of Mucinous Carcinoma

Many cases of ovarian mucinous carcinoma are clinical stage I or II, and most cases undergo complete surgical resection. Therefore, the prognosis associated with early cases is favorable [20]. In a clinical study reported by the US Gynecologic Oncology Group (GOG), the outcome of clinical stage III epithelial ovarian cancer in patients who received paclitaxel and carboplatin (TC) chemotherapy was the poorest compared to those of other histologic types of mucinous carcinoma [21]. Moreover, anticancer drug sensitivity was low and survival time was short compared to those of high-grade serous carcinoma patients in many reported studies [22,23]. Because this cancer has a low sensitivity to existing TC chemotherapy, a new chemotherapy regimen is being investigated. In 2003, Seidman et al. reported that 77% of pathologically diagnosed mucinous carcinoma cases were metastases from multiple organs, which was very surprising [24].

Based on the concept that mucinous carcinoma is similar to gastrointestinal cancers, such as colorectal and gastric cancers, clinical studies were performed using the chemotherapy regimen for gastrointestinal cancers. The Japan Ovarian Mucinous Adenocarcinoma Study Group performed a phase II study using SOX chemotherapy (S-1, oxaliplatin) for advanced and recurrent mucinous carcinomas. According to its interim report, the central pathological diagnosis was primary mucinous carcinoma in 14 out of 40 patients, and metastatic mucinous carcinoma from primary lesions occurred in the pancreas, stomach, and large intestine of 19 patients, accounting for nearly half of the patients. Seven patients were diagnosed with ovarian cancer rather than with mucinous carcinoma. The diagnosis rate for primary mucinous carcinoma was 35%, indicating difficulty in making a diagnosis, which supports the findings reported by Seidman et al. The response rate of all mucinous carcinoma cases to chemotherapy was 12.1%, and the disease control rate was 69.6%. The response and disease control rates of primary mucinous carcinoma cases were 0 and 64.2%, respectively, and those of metastatic mucinous carcinoma cases were 21 and 73.6%, respectively. It was concluded that approximately 50% of advanced and recurrent ovarian mucinous carcinoma cases were metastatic tumors and that SOX chemotherapy might contribute to the improvement of the overall survival time [25] (Figure 3).

Molecular-Biological Characteristics of Mucinous Carcinoma

Molecular-biological studies on ovarian mucinous carcinoma concerning histologic types are limited, which is clinically attributable to its low incidence rates (approximately 3-10%). The frequency of *KRAS* gene mutations was 75% [26], and the presence of *KRAS* mutations in mucinous cystadenoma and mucinous borderline tumors, assumed to be precancerous lesions, was reported [27]. Therefore, it was suggested that carcinogenesis occurred through the adenoma-carcinoma sequence over a long period.

The *p53* mutations observed in type II ovarian cancers and *BRAF* mutations observed in low-grade serous carcinoma are absent in mucinous carcinoma [28]. We also previously performed comprehensive allelotype analysis of mucinous and serous borderline tumors [29]. In Japan, the frequency of the mucinous type is very high in borderline tumors (mucinous: serous=5:1), suggesting that the carcinogenesis mechanism of ovarian cancers is different from that in the western population [30]. Deleted regions are distributed

throughout all chromosomes on mucinous borderline tumors, whereas deletions are concentrated on some chromosomes in serous borderline tumors. Based on this, we paid attention to differences in the mechanism of carcinogenesis between the histologic types [29].

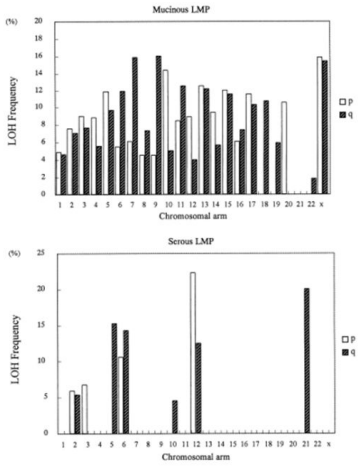

Figure 2

Figure 3: Difference in the allelotype between mucinous and serous borderline tumors. (Figure adapted from [25]). (LMP: Low malignant potential = border line tumor).

It was recently reported that the frequency of *HER2* gene amplifications in mucinous carcinoma was 18.3% among the western population [4] and 35.3% among Asians [31], suggesting that *HER2*-targeting molecular-targeted therapy is effective. Indeed, McAlpine et al. administered trastuzumab in addition to standard chemotherapy to 3 patients with mucinous carcinoma, and observed a marked effect in 1 patient [4]. Currently, we are performing whole exosome analysis of mucinous carcinoma as a rare tumor sequence in a cooperative study with Johns Hopkins University, investigating the presence of a new gene aberration.

Prospects of Molecular Targeting Drugs

We previously reported that *MAPK* signals are constitutively activated in an ovarian cancer cell line possessing *KRAS/BRAF* mutations, and MEK1/2 inhibitor exhibited a marked effect at the cellular level and in a nude mouse transplantation model [12]. A phase II study using selumentinib (AZD6244, ARRY142866), a MEK1/2 inhibitor, was recently conducted by the US (GOG) in patients with recurrent low-grade serous carcinoma [28].

Fifty-two patients were enrolled and continuously received 50 mg of oral selumentinib twice daily until disease progression was observed; 4-week administration was regarded 1 cycle. Interestingly, complete remission (CR) and partial remission (PR) were noted in 1 and 7 patients, respectively, and the response rate was 15.4%. Stable disease (SD) was observed in 34 (65.4%) patients, and the disease control rate was 80.8%. The median aggravation-free survival time was 11.0 months, and a 6-month or longer aggravation-free period was achieved in 63.5% (33/52) of patients. No death related to adverse events was reported. Unfortunately, no correlation was noted between the *KRAS*/*BRAF* mutation and response rate, and the diagnostic value of the *KRAS*/*BRAF* mutation remains unclear [32]. No clinical study of a molecular-targeted drug for mucinous carcinoma has been reported; however, molecular-biologically, a therapeutic strategy using MEK1/2 inhibitors might be possible, similar to that for low-grade serous carcinoma, because of the high *KRAS*- and low *p53*-mutation rates. Treatment with trastuzumab is also expected because the frequency of human epidermal growth factor receptor (*HER) 2* gene amplification is high in mucinous carcinoma [4].

Conclusion

Both low-grade serous carcinoma and mucinous carcinoma are low sensitive to existing anticancer drugs, causing problems for clinicians. They have not been widely studied due to low incidence rates. However, with recent advances in molecular biology, the efficacy of *KRAS*/*BRAF*/MAPK signal-targeted treatment was shown in a preclinical study and the efficacy of selumentinib (AZD6244, ARRY142866), a MEK1/2 inhibitor, was shown in a phase II clinical study. Carcinogenesis mechanism-based personalized treatment might improve the outcome in the future.

We are now attempting to establish immortalized ovarian serous cystadenoma and mucinous adenoma cells, and the construction of an *in vitro* carcinogenesis model for type I ovarian cancer pathway is underway. This carcinogenesis model is expected to provide a basis for the development of molecular-targeted therapies of low-grade serous carcinoma and mucinous carcinoma.

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