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Original Article

Inhibitory role of prohibitin in human ovarian epithelial cancer

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Abstract: Objectives: To characterize the exact individual roles of gonadotropins on ovarian epithelial carcinogenesis, an earlier study showed that prohibitin was significantly up-regulated by luteinizing hormone (LH). To further clarify the role of prohibitin in ovarian carcinogenesis and its association with LH, herein we studied the expression of prohibitin in various ovarian tissues including different developmental stages of ovarian epithelial tumors. Methods: A total of 135 samples were studied by immunohistochemistry. These included benign ovarian cases with follicles, ovarian surface epithelia and ovarian epithelial inclusions (OEI) (n=30), serous cystadenoma (n=14), serous borderline tumor (n=12), serous carcinoma (n=20), mucinous cystadenoma (n=10), mucinous borderline tumor (n=10), mucinous carcinomas (n=10), endometrioid carcinomas (n=12), poorly/undifferentiated carcinomas (n=5), and fallopian tube (n=12). Results: Strong and diffuse staining of prohibitin was detected in luteinized ovarian stromal cells, follicular cells, fallopian tube, and OEI with serous differentiation. A significantly higher prohibitin expression in luteinized stromal cells than in non-luteinized stromal cells was observed ($P<.01$). Within the ovarian epithelium, the level of prohibitin expression was basically negative in ovarian surface epithelia, but highly expressed in OEI. However, compared to the level of prohibitin expression in OEI, it showed a trend of gradual loss from benign ovarian tumors, to borderline tumors and to carcinomas ($P<.0001$). Compared to the serous tumors, epithelial tumors with mucinous differentiation showed a significant lower level of prohibitin ($P<.0001$). An inverse correlation was noted between prohibitin expression and cancer grade. It is interesting to note that a high prohibitin expression level was seen in the fallopian tube, which is similar to OEI. Conclusions: These data further suggest that prohibitin plays a tumor suppressing role, which is probably associated with LH mediated protection role against ovarian epithelial carcinoma. In addition to the tumor suppressive role of prohibitin, it also plays a role in cellular differentiation, which may be helpful to differentiate ovarian mucinous tumors from the tumors with serous differentiation in clinical settings. More importantly, our findings are supportive that the ovarian epithelial cancers, particularly the serous cancers including those precursors with serous differentiation are likely to be derived from fallopian tube instead of ovarian surface epithelia.

Keywords: Gonadotropin, luteinizing hormone, prohibitin, ovarian cancer

Introduction

Ovarian cancer ranks the first leading cause of death among gynecologic malignancies. In 2013, an estimated 22,240 new cases will be diagnosed and 14,030 deaths from ovarian cancer will occur in the United States [1]. Usually more than two thirds of the patients present at advanced stage and have an overall 5-year survival of 30%. Hence, the poor prognosis could be improved by a better understanding of its molecular pathogenesis, which may ultimately contribute to identification of new biomarkers useful for its early detection, and development of individualized therapies.

Ovarian epithelial carcinoma (OEC), the most common histologic type of ovarian cancer, is a

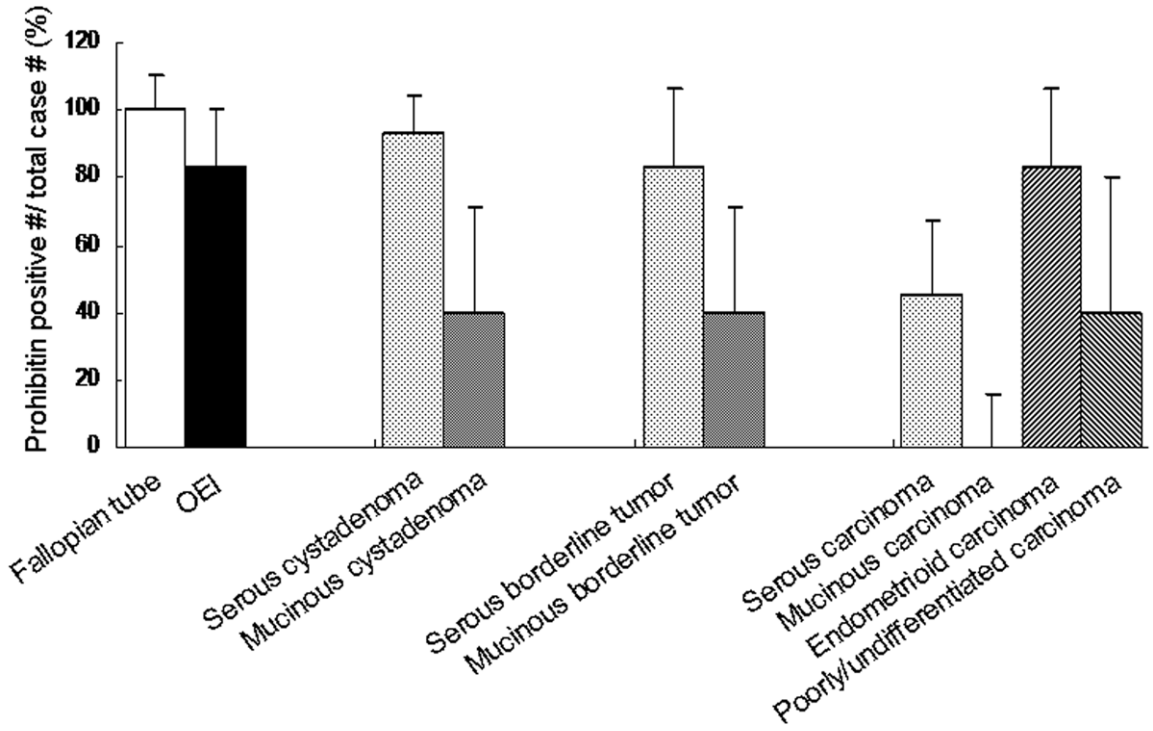

Figure 1. Prohibitin expression in various ovarian tissues and fallopian tube. Prohibitin expression was decreased steadily from fallopian tube (100%) to OEI (83%) including both endosalpingiosis and endocervicosis, to benign ovarian tumors (71%), to borderline tumors (64%) and to carcinomas (45%).

heterogeneous disease. There have been several theories to explain the etiology of sporadic OEC, including theories of gonadotropins, incessant of ovulation, sex-steroid hormone, and pelvic chronic inflammation. The gonadotropin theory proposes that the development of OEC is related to elevated gonadotropin production. To characterize the individual roles of gonadotropins in the development of OEC, we previously demonstrated that luteinizing hormone (LH) might be inhibitory for ovarian epithelial tumor (OET) cell growth, further evidenced by a novel identification of prohibitin, which is a potential tumor suppressor and particularly up-regulated by LH [2]. As the main gonadotropin responsive organ, ovary is expected to express prohibitin since it is responding to LH stimulation [3]. Although the cell origin or histogenesis of OEC has been currently shifted from ovarian surface epithelia to the fallopian tube [4, 5], debate remains [6, 7]. Therefore, in order to examine if prohibitin expression in human ovarian epithelium matches current understanding of OEC development and histogenesis, we examined prohibitin expression in various human ovarian tissue and fallopian tubal samples by immunohistochemistry (IHC).

Materials and methods

Tissue sections and pathologic features of studied cases

All evaluated ovarian tissue samples were derived from Department of Pathology at the University of Arizona and the study was approved by an Institutional Review Board. Hematoxylin and Eosin (H&E)-stained slides from a total of 147 cases were reviewed, characterized and studied. These included 12 benign fallopian tube samples, 30 benign ovaries with follicles and ovarian epithelial inclusions (OEI), which is also called as endosalpingiosis, 14 serous cystadenomas, 10 mucinous cystadenomas, 12 serous borderline tumors and 10 primary mucinous borderline tumors, and 47 ovarian carcinomas. Among the 30 benign ovaries, we examined prohibitin expression in developing follicles (n=7), non-luteinized stroma (n=8), luteinized stroma including ovar-

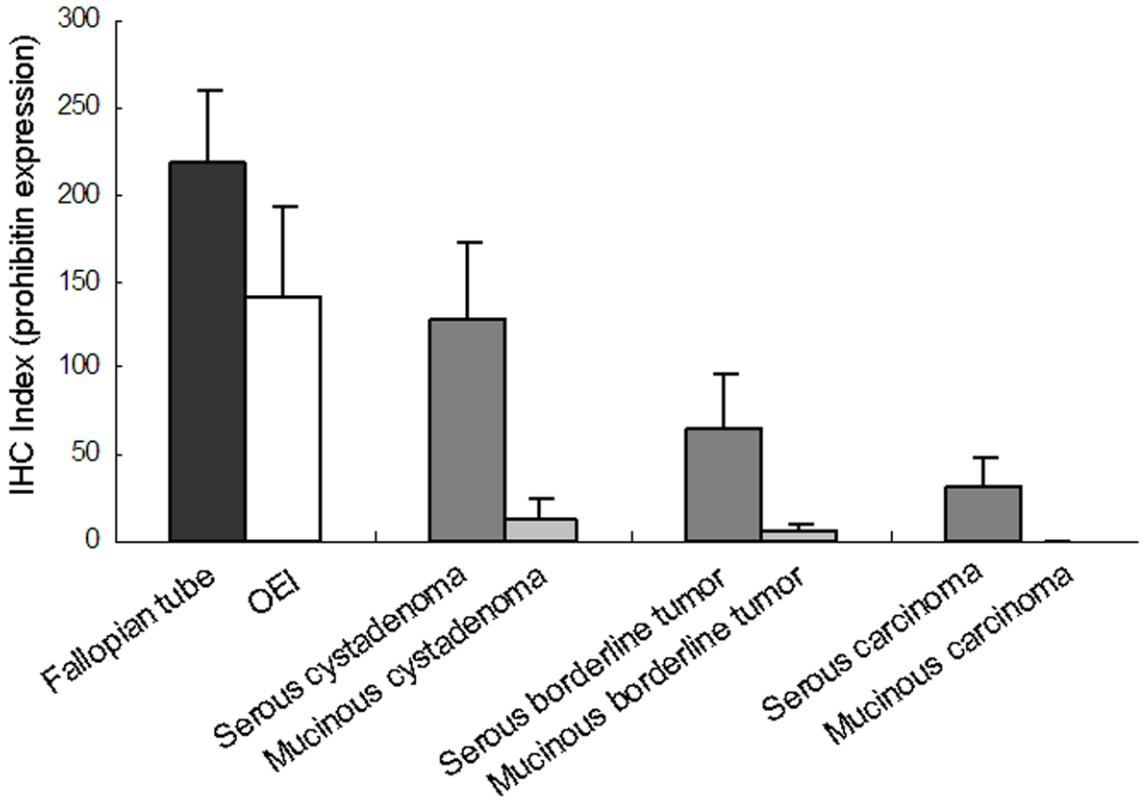

Figure 2. Prohibitin expression in ovarian epithelium with serous and mucinous differentiation. Prohibitin was expressed in all 12 fallopian tube samples and in most of the 23 OEIs (14/14 with serous differentiation and 5/9 with mucinous differentiation). A trend of reduction was observed from cystadenoma to borderline tumors, and to carcinomas.

ian hilar cells (n=8), ovarian surface epithelium (OSE) (n=16), OEI with serous differentiation (n=14), and OEI with mucinous differentiation (n=9). Some ovaries contained more than one targeted areas, therefore, the total number of benign areas studied exceeded 30. Among the ovarian cancer cases, we examined prohibitin expression in serous (n=20), mucinous (n=10), endometrioid (n=12), and poorly/undifferentiated (n=5). The mucinous carcinomas were all ovarian primary by clinicopathologic studies (data not shown). Of all carcinomas, the serous carcinomas had grade 1 (n=6), grade 2 (n=5) and grade 3 (n=9); the mucinous carcinomas had grade 1 (n=3), grade 2 (n=2), and grade 3 (n=5); and endometrioid carcinomas had grade 1 (n=3), grade 2 (n=3), and grade 3 (n=6). Prohibitin expression in 14 serous cystadenomas, 12 serous borderline tumors, and 20 serous carcinomas has been reported in our previous study [2]. All malignant cases were diagnosed and graded using criteria of the International Federation of Obstetrics and Gynecology (FIGO) [8].

Immunohistochemistry

IHC stains were performed on 5-μm tissue sections from representative blocks using the purified mouse anti-prohibitin antibody and the standard avidin-biotin-complex technique as described previously [9, 10]. Briefly, sections from routinely processed, formalin-fixed, paraffin-embedded tissues were transferred to glass slides, dried at 58°C for 60 minutes, deparaffinized with xylene and dehydrated with graded ethanol rinses, and washed with tap water. Microwave antigen retrieval (770 watts, 14 minutes) was performed following immersion in citrate buffer (0.01 M, pH 6.0). The slides were cooled, rinsed with PBS (3 rinses, 5 minutes each), and stained on the Ventana Autostainer (Ventana, Tucson, AZ) at room temperature. Endogenous peroxidase activity was blocked

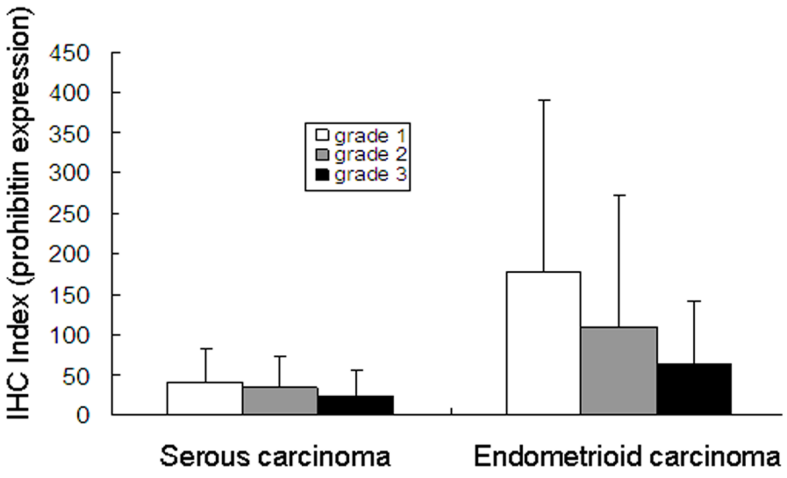

Figure 3. Prohibitin expression in serous and endometrioid carcinomas. The expression index was negatively associated with cancer grade.

with 3% hydrogen peroxide, and the slides were rinsed and treated with a blocking protein (Ventana, Tuscon, AZ) to prevent non-specific staining. The sections were then incubated with anti-prohibitin mouse monoclonal antibody (Ready-to-Use). The antibodies had been tittered to avoid background staining and when optimal cytoplasmic staining was reached. After brief washes, the sections were treated with a cocktail of biotinylated anti-rabbit IgG and anti-mouse IgG/IgM (Ventana) for 30 minutes. Then they were washed, and incubated with avidin/biotin/peroxidase complex (Ventana) for 30 minutes, and were rinsed, developed with diaminobenzidine and hydrogen peroxide (10 minutes), and counterstained with Mayer's hematoxylin and mounted.

Evaluation

Positive and negative controls were included as described previously [2]. For those cases containing multiple target areas (such as ovarian surface epithelium, ovarian inclusions, and ovarian stroma in cases of benign ovaries), each of the foci was separately evaluated. All IHC slides were reviewed independently by two investigators (WZ and YW). The percentage of neoplastic cells and non-neoplastic tissues that showed dark brown cytoplasmic staining was recorded. The staining intensity was graded for both on the following scale: 0=no staining; 1=weak staining; 2=moderate staining; and 3=intense staining. Prohibitin IHC index was generated by multiplying the intensity by the percentage of positive cells in a defined specimen, yielding scores ranging from 0 to 300. Stained cells exceeded 10% were considered positive and stainings were performed in duplicate.

Statistical analysis

The comparison of prohibitin staining index scores among different types of ovarian tissue were performed using the Wilcoxon signed rank test for the paired samples and the exact Wilcoxon two-sample rank-sum test for the unpaired samples. The comparisons of prohibitin positivity by pathological characteristics were assessed by the Chi-square test. Data are presented as means with 95% confidence intervals (CIs). Statistical analysis was performed by using SAS 9.0 (SAS Institute Inc, Cary, NC). A two-sided test with *P* values of less than .05 was considered statistically significant.

Results

Prohibitin expression in benign non-epithelial ovarian tissue

Ovarian sections containing secondary follicles (n=4), graafian follicles (n=3), luteinized stroma without follicles (n=8) and non-luteinized stroma (n=8) were evaluated. Prohibitin was detected in all follicles and ovarian stroma. Within ovarian follicles, expression of prohibitin was strong and diffuse in both granulose and theca interna cells. Within the non-follicular ovarian stroma, prohibitin expression was high in luteinized ovarian stroma. In contrast, in non-luteinized ovarian stroma, although positive prohibitin staining was seen in all cases, the IHC scores were significantly lower than those in luteinized ovarian stroma and ovarian follicles (*P*<.001).

Prohibitin expression in OSE, OEI and fallopian tube

A total of 16 OSE, 23 OEIs and 12 fallopian tube samples were evaluated. Prohibitin was expressed in 2 of the 16 OSE samples. Within the 23 OEIs, 14 were lesions of endosalpingio-

Table 1. Prohibitin Expression in Relation to the Characteristics of Ovarian Tissues

Ovarian Tissues	Prohibitin Positivity	Prohibitin Index		
	Positive#/total case # (%)	Range	Mean	95% CI
Benign non-epithelial ovarian tissue				
A. Granulosa cells	7/7 (100)	100-300	234	165-303
B. Theca interna cells	7/7 (100)	200-300	271	226-317
C. Luteinized stroma	8/8 (100)	200-300	288	258-317
D. Non-luteinized stroma	8/8 (100)	5-60	29	14-45
Non-neoplastic epithelium				
A. Fallopian tube	12/12 (100)	100-300	219	178-261
B. OSE	2/16 (13)	0-50	30	5-40
C. OEI	19/23 (83)	0-300	140	88-193
a. Endosalpingiosis	14/14 (100)	90-300	219	168-269
b. Endocervicosis	5/9 (56)	0-50	19	3-35
Neoplastic epithelium				
A. Cystadenomas	17/24 (71)	0-300	83	48-117
a. Serous	13/14 (93)	0-300	129	89-175
b. Mucinous	4/10 (40)	0-40	13	0.4-26
B. Borderline tumors	14/22 (64)	0-150	38	17-59
a. Serous	10/12 (83)	0-150	66	35-97
b. Mucinous	4/10 (40)	0-20	6	0-11
C. Carcinomas	21/47 (45)	0-270	42	24-61
a. Serous	9/20 (45)	0-120	31	12-49
b. Mucinous	0/10 (0)	0	0	0-0
c. Endometrioid	10/12 (83)	0-270	103	50-156
d. Poorly/undifferentiated	2/5 (40)	0-120	28	0-93
OEC grade				
A. Grade 1	6/9 (67)	0-270	86	18-154
a. Serous	3/6 (50)	0-100	40	0-88
b. Endometrioid	3/3 (100)	100-270	177	0-391
B. Grade 2	6/8 (75)	0-180	63	14-111
a. Serous	3/5 (60)	0-70	34	0-74
b. Endometrioid	3/3 (100)	50-180	110	0-273
C. Grade 3	7/15 (47)	0-200	39	6-71
a. Serous	3/9 (33)	0-120	22	0-55
b. Endometrioid	4/6 (67)	0-200	63	0-141

Prohibitin index: obtained from the summary of the percentage of positively stained cells and staining intensity. OSE: ovarian surface epithelium; OEI: ovarian epithelial inclusion; OEC: ovarian epithelial cancer.

sis (OEI with serous differentiation) and 9 were endocervicosis (OEI with mucinous differentiation). Prohibitin expression was found to be positive in all endosalpingiosis. However, prohibitin expression was positive in only 5 of 9 lesions of endocervicosis with the mean score of 19, which was significantly lower than that in endosalpingiosis (P<.0001). It is interesting to note that prohibitin was highly expressed in all fallopian tube samples. Compared with OSE and OEI samples, prohibitin expression in fallopian tube was significantly higher (P<.0001), but showed no difference from OEI.

Prohibitin expression in neoplastic ovarian tissue

Previously we have demonstrated prohibitin expression in tissues of serous cystadenomas, borderline tumors and carcinomas and repeated results were confirmed in current study. Herein expanded investigation found that in the mucinous cystadenoma category, prohibitin expression was positive in 4 of 10 cases, which was significantly lower than that in serous cystadenomas (P<.0001). In borderline epithelial ovarian tumors, the tumor with mucinous differentiation was positive in 4 of 10 cases, which was again significantly lower than that in serous borderline tumors (P =.002). Among the 47 OEC studied cases, no prohibitin expression was identified in mucinous cancers. While within the endometrioid carcinoma category, prohibitin was found to be positive in 10 of 12 cases, which was significantly higher than in serous carcinomas (P=.008). Prohibitin was found positive in 2 of 5 poorly differentiated carcinomas.

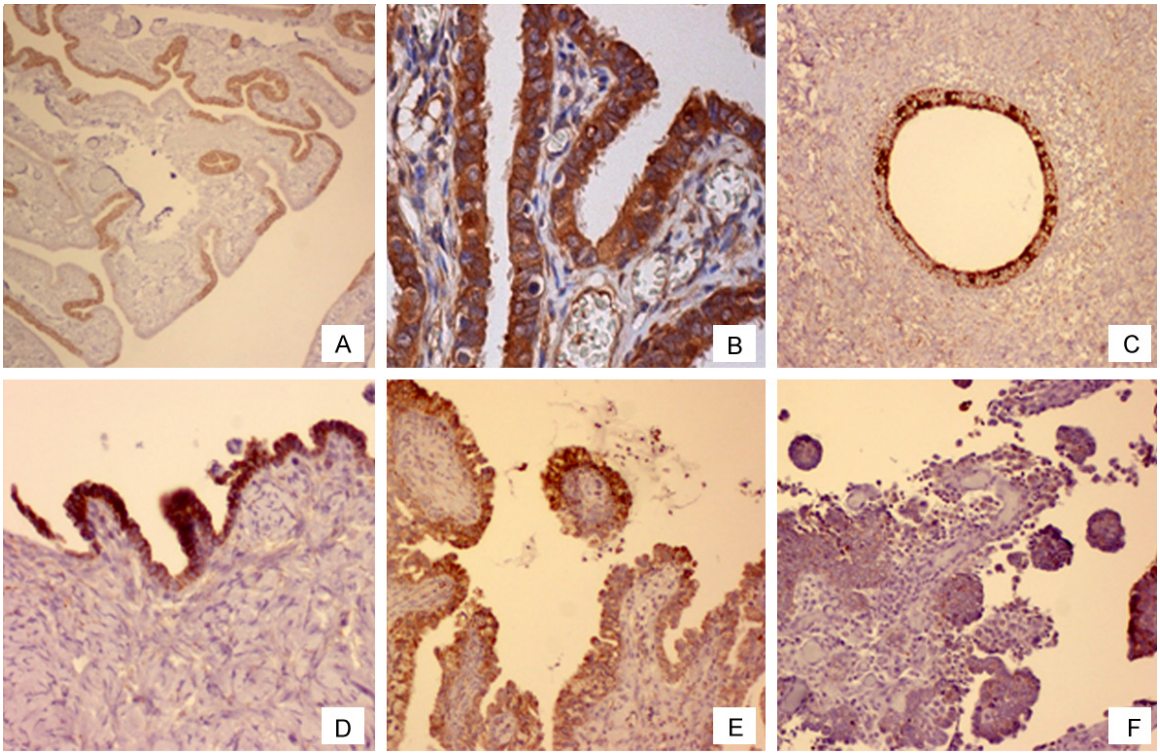

Figure 4. Representative immunohistochemical staining for prohibitin. Prohibitin staining detected strong positive signals (dark brown) in fallopian tube (A, 40x and B, 200x), areas of OEI with serous differentiation (endosalpingiosis) (C, 100x), and serous cystadenomas (D, 100x). In contrast, weaker signal was detected in serous borderline tumors (E, 200x); while mostly negative in high-grade serous carcinomas (F, 200x).

In summary, prohibitin expression was basically unanimous in benign ovarian tissues with the highest expression in luteinized ovarian stromal cells, follicular cells, fallopian tube, and OEI with serous differentiation. In contrast, the prohibitin expression was mainly negative in OSE samples. Compared to all the ovarian epithelial samples and fallopian tube cases, we have found that prohibitin expression level was decreased steadily from fallopian tube (100%) to OEI (83%) including both endosalpingiosis and endocervicosis, to benign ovarian tumors (71%), to borderline tumors (64%) and to carcinomas (45%) (**Figure 1**). The trend of reduction of prohibitin expression was statistically significant ($P<.0001$). Among the epithelial samples with mucinous differentiation, prohibitin was found in 13 of the total 39 cases, which was significantly lower than those in epithelia with either serous or endometrioid differentiation (**Figure 2**) ($P<.0001$). While compared to the tumors with serous differentiation, the prohibitin level of expression was higher in those with endometrioid differentiation. Within the carcinoma category, prohibitin expression was negatively associated with cancer grade. This trend of reduction was mainly seen in serous and endometrioid carcinomas (**Figure 3**). Mucinous carcinoma was mainly negative for prohibitin expression. In non-epithelial benign ovarian tissue, both granulosa and theca cells in ovarian follicles were highly positive for prohibitin expression with no statistical difference. This is sharply in contrast with ovarian stroma. A significantly higher prohibitin expression in luteinized stromal cells than in non-luteinized stromal cells was observed ($P<.01$). The data are summarized in **Table 1**. Representative pictures of prohibitin IHC in ovarian tissues and fallopian tube are presented in **Figure 4**.

Discussion

In addition to confirm our previous finding of tumor suppressive role of prohibitin in ovarian epithelial carcinogenesis [2], this study revealed something interesting in the following aspects.

First of all, the prohibitin expression may be regulated or controlled by LH. It is known that folliculogenesis is a gonadotropin dependent

process [11] and LH is the key hormone to induce ovulation [12]. The main cellular effect of LH in ovarian non-epithelial tissue is to induce luteinization. This is correlated to the high level of prohibitin expression was found in luteinized ovarian stromal cells as well as in the theca interna cells of the follicles, while non-luteinized ovarian stromal cells were basically no prohibitin expression. Apparently, ovarian stromal cells are different from epithelial cells, particularly different from epithelial tumor cells [13]. However, prohibitin is a unique biomarker which expresses both in specialized stromal cells as well as in ovarian epithelial tumor cells. This unique expression pattern parallels to the LH expression pattern. We have shown that LH receptors are expressed in the ovarian epithelial tumors in the past and suggested that LH has a tumor suppressive role in ovarian epithelial carcinogenesis [3]. Our current study showed that the prohibitin expression was gradually lost from benign to borderline tumors and to carcinomas, from low- to high-grade, and from low- to high-stage ovarian cancers. This interesting clinicopathologic finding clearly indicates that prohibitin plays a tumor suppressive role in the process of ovarian epithelial carcinogenesis. Loss of prohibitin expression may promote the cancer development. In combination with our previous finding on the tumor suppressive role of LH in ovarian cancer, we speculate that the tumor suppressive role of LH is likely to be carried out through prohibitin expression in targeted cells.

Second, prohibitin may have a cellular differentiation function in ovarian epithelial tumor. Differential prohibitin expression was clearly demonstrated in both non-neoplastic and neoplastic ovarian epithelia in this study. One of the striking observations from our study was the prohibitin was significantly higher in endosalpingiosis (ovarian epithelial with serous differentiation) than that in endocervicosis (ovarian epithelia with mucinous differentiation). Furthermore, with the ovarian epithelial tumor category, prohibitin expression in mucinous tumors was significantly lower than that in serous and endometrioid tumors (**Table 1**). From this perspective, loss of prohibitin seems to be associated with mucinous differentiation in ovarian epithelial cells. This was demonstrated by the findings that prohibitin was diffusely positive in area of serous epithelium (portion of endosalpingiosis) but abruptly negative in area of mucinous differentiation (portion of endocervicosis) in the same lesion of OEI. Such observations suggest that prohibitin may function as an ovarian epithelial cell differentiation factor, which may contribute the diversification of many histopathologic types of ovarian epithelial tumors. It is currently unclear whether scarce prohibitin expression in mucinous tumors is indicative of less LH-dependent because of presence of less LH receptors in mucinous tumor cells [3] and such phenomenon is related to the less protection observed in mucinous tumors from oral contraceptive use than in other histological subtypes [3, 14]. Considering presence of various prohibitin expression pattern in different stage of OET development and in different histologic type of OEC, it is worth to explore its prognostic and diagnostic roles in future.

Third, prohibitin expression levels in the fallopian tube, ovarian epithelial inclusions and ovarian surface epithelia supports that ovarian cancers are likely derived from fallopian tube rather than from ovarian surface epithelia. The cell origin of ovarian cancer is among the least understood of all major human malignancies. With much evidence and ongoing studies, the fallopian tube has emerged as the probable site of ovarian serous tumors. Doran *et al.* [15] was the first to note the fallopian tube as a possible origin in 1896 but his theory was disregarded until Piek *et al.* [16, 17] again described the fallopian tube as a possible suspect [18, 19]. The topic was fully revived after the work of Crum *et al.* [20-22] showed that serous carcinoma precursor lesions in BRCA patients were mostly located in the fimbriated ends of the fallopian tube [19, 23]. In fact, studies have shown that the most distal fimbriated end of the fallopian tube is the preferred site, irrespective of *BRCA* mutations, for early tumor growth and that 70% of serous carcinomas involve the endosalpinx [22]. Therefore, ovarian epithelial tumors, particularly serous carcinomas are likely derived from fallopian tube. However, debates remain. An emerging theory from the efforts of Seidman *et al*. suggests that the instead of the fimbriated end, it is the tubal-peritoneal fimbrial junction (TPJ) that could be the origin of the neoplastic cells [23]. Their group notes that epithelial/mesothelial junctions such as those in the cervical, gastrointestinal and anorectal

areas are well known perpetrators of dysplastic change. Our current study showing the evidence of high level prohibitin expression in fallopian tube and OEI with serous differentiation, but not in OSE supports that ovarian serous tumors are likely to be tubal origin. Such findings are also consistent with our recent reports of secretory cells within the fallopian tube are the cells to form OEI, and then ovarian serous tumors [4, 24, 25]. It would be interesting to know if prohibitin may play a role in populating the tubal secretory cells in the process of ovarian serous carcinogenesis.

Taken together, these data further suggest that prohibitin plays a tumor suppressing role, which is probably associated with LH mediated protection role against OEC. In addition, prohibitin may also play a role in cellular differentiation. Such cellular differentiation function may be helpful to differentiate ovarian mucinous tumors from the tumors with serous differentiation in clinical settings. More interestingly, our findings are supportive that the ovarian epithelial cancers, particularly the serous cancers including those precursors with serous differentiation are likely to be derived from fallopian tube instead of ovarian surface epithelia. Future studies on the molecular mechanism of prohibitin in the growth advantage of tubal secretory over ciliated cells will be interested in the field.

Acknowledgements

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Disclosure of conflict of interest

We declare that we have no conflict of interest.

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