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HMGA2: A biomarker significantly overexpressed in high-grade ovarian serous carcinoma

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Ovarian carcinoma consists of a group of histologically heterogeneous diseases involving distinct tumorigenic pathways. High-grade papillary serous carcinoma of the ovary is commonly associated with *p53* mutations. *HMGA2*, an oncofetal protein, is found to be overexpressed in ovarian cancer. To study the function of *HMGA2* in ovarian cancer, it is important to know which subtypes of ovarian cancer are associated with *HMGA2* overexpression. In this study, we collected six different types of ovarian cancer and examined *HMGA2* expression by immunohistochemistry, along with *HMGA1*, *p53* and *Ki-67*. We found that *HMGA2* overexpression was significantly higher in high-grade papillary serous carcinoma (64%) and carcinosarcoma (60%) than in other types of ovarian cancers (7–23%). *HMGA2* overexpression was moderately associated with dominant *p53* mutations ($R = 0.51$). In addition, the microRNA *in situ* analysis revealed that *let-7b*, the *HMGA2*-negative regulators, were significantly lost in high-grade serous carcinoma. Our findings suggest that *HMGA2* is an important molecular change significantly related to high-grade papillary serous carcinoma and is less common in other histological types of ovarian cancer.
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Epithelial ovarian cancer accounts for about 3% of total cancer cases in women. However, ovarian cancer is one of the most lethal gynecological malignancies. An estimated 21,550 new cases were expected in the United States in 2008. An estimated 15,520 deaths were expected in 2008.[1] Ovarian cancer is a group of heterogeneous diseases and consists of different histological types, which can be readily differentiated by histological evaluation. Genome-wide global gene analysis further defines distinct expression profiles of different types of ovarian cancer.[2] Different histological types of ovarian cancer seem to be regulated by different pathogenic pathways.[3]

HMGA2, a high-mobility-group AT-hook (HMGA) protein, is a nonhistone DNA-binding factor and binds to AT-rich sequences in the minor groove of the DNA helix. *HMGA2* is expressed in embryonic tissue, but not in most adult tissues,[4,5] and is an important regulator for cell growth, differentiation, apoptosis and malignant transformation.[6]

HMGA2 is overexpressed in many malignant neoplasms,[6] including ovarian cancer.[7–10] In animal models, overexpression of *HMGA2* is found to be an early event in ovarian tumorigenesis.[7,9] Studies have shown that silencing of *HMGA2* gene expression prevents *RAS*-induced transformation of thyroid cells,[11] inhibits ovarian cancer growth in nude mice[7] and results in growth inhibition and increased apoptosis of liposarcoma cells.[12] *HMGA2* may be an important tumorigenic factor associated with cancer development. The expression of *HMGA2* is regulated by microRNA. Studies show that *let-7s* can specifically repress *HMGA2* expression both *in vivo* and *in vitro*, revealing the regulatory role of *let-7* in *HMGA2* expression.[9,13–17] Downregulation of *let-7s* is common in ovarian cancer.[16,18]

To understand the function of *HMGA2* in human ovarian cancer, it is important to characterize which type of ovarian cancer is associated with *HMGA2*

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overexpression. In this study, we examined *HMGA2* expression along with *HMGA1*, *p53* and *Ki-67* in various types of ovarian cancer. Our results show that *HMGA2* overexpression was significantly higher in high-grade papillary serous carcinoma than in other types of ovarian cancer. In addition, we found that *let-7b*, the negative regulator of *HMGA2*, was significantly downregulated in high-grade papillary serous carcinoma. We suggest that *HMGA2* can be one of the important molecules in the tumorigenesis of high-grade papillary serous carcinoma.

Materials and methods

Case Selection

The cases were collected after surgery at Northwestern Memorial Hospital and New York University from 1996 to 2009. Approval of the institutional research board from both institutions was obtained. A total of 115 cases of ovarian cancer were collected for the study. This included histological diagnosis of high-grade papillary serous carcinoma ($N=30$), serous borderline tumor ($N=10$), malignant mixed Mullerian tumor (carcinosarcoma, $N=15$), endometrioid ovarian carcinoma ($N=30$), mucinous ovarian carcinoma ($N=15$) and clear cell ovarian carcinoma ($N=15$). Patients' ages at surgery, tumor sizes, FIGO grades and stages and lymph node metastasis are summarized in Table 1.

Table 1 Clinical summary of the different types of ovarian carcinoma in this study

	HG-PSC	*SBT*	*MMMT*	*EOC*	*MOC*	*CCOC*
Age						
Average	66	47	67	55	46	57
Range	40–93	28–73	51–88	36–71	18–93	34–85
Tumor size (cm)						
$<=5$	6	4	6	2	0	5
5.1–20	28	5	8	7	7	8
>20	0	1	0	1	8	0
FIGO grade						
Low	10	0	3	15	0	
Moderate	3	0	0	3	0	3
High	26	0	10	4	0	5
FIGO stage						
I	0	5	0	12	15	7
II	2	0	4	9	0	0
III	27	3	11	9	0	4
IV	0	0	0	0	0	0
Lymph nodes						
Positive	19	2	3	0	0	1
Negative	11	8	12	9	7	6
No. of cases	30	10	15	30	15	15

CCOC: clear cell ovarian carcinoma; EOC: endometrioid ovarian carcinoma; HG-PSC: high-grade papillary serous carcinoma; MMMT: malignant mixed Mullerian tumor; MOC: mucinous ovarian carcinoma; SBT: serous borderline tumor.

Tissue Preparation, Antibodies and Immunohistochemistry

All cases were reviewed by two pathologists. Tissue cores were collected from tumor and control sections of each case (normal fallopian tubes for serous carcinoma, endometrium for endometrioid carcinoma) for tissue microarray. Antibodies used for this study included *HMGA1* (kindly provided by Dr E Hernando), *HMGA2* (BioCheck Inc., Foster City, CA, USA), *Ki-67* (cell proliferation marker; Neomarkers, Fremont, CA, USA) and *p53* (Dako, Carpinteria, CA, USA). Tissue microarrays were sectioned 4 μm in thickness. After deparaffinization and antigen retrieval, all immunohistochemical staining was performed on a Ventana Nexus automated system (Tucson, AZ, USA). In brief, endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Primary antibodies were detected using standard biotinylated anti-mouse or anti-rabbit secondary antibodies.

let-7b and *let-7c* microRNA *In Situ* Hybridization

The hybridization system and probes of miRCURY LNA, including *let-7b*, *let-7c* and *U6*, were purchased from Exiqon (Vedbaek, Denmark). The detailed procedure for *in situ* hybridization was followed as per manufacturer's protocol.[19] In brief, 4 μm tissue microarray slides were prepared. After deparaffinization and deproteinization, the slides were prehybridized with 1 $\times$ hybridization buffer without probe. The hybridization was carried out overnight in a 1 $\times$ hybridization buffer (30–70 μl) with predenatured miRCURY LNA, *let-7b*, *let-7*c or *U6* probes. After washing, the slides were blocked and incubated with AP-conjugated anti-DIG Fab fragments (1:1500; Roche, Indianapolis, IN, USA) and visualized for color detection.

Immunoscores, MicroRNA Scores and Statistical Analysis

One-score system for immunointensity and microRNA intensity was used for the markers *HMGA1*, *HMGA2* and *p53*, and microRNA *let-7b* and *let-7c*. The semiquantitation for intensity was scored on a scale of 0, negative; 1, weak; 2, moderate and 3, strong. Another score system for percentage of immunopositivity was used for *Ki-67* that was immunoreactive for only a portion of the tumor cells. The mean values and standard errors were calculated. Paired *t*-test was used. The *P*-values <0.05 were considered as statistically significant.

Results

Expression of *HMGA2* in Different Types of Ovarian Cancer

In this study, we collected a total of 115 ovarian carcinomas from 6 different histological types,

including high-grade papillary serous carcinoma, carcinosarcoma, serous borderline tumor, endometrioid ovarian carcinoma, mucinous ovarian carcinoma and clear cell ovarian carcinoma. In addition, sections from normal fallopian tubes and normal endometrium were collected as normal control. The detail biomedical factors of these tumor types are summarized in Table 1.

HMGA2 was weakly and occasionally moderately expressed in ciliated cells of fallopian tube, but completely negative in secretory cells and endometrial stromal and epithelial cells (data not shown).[20] In tumor sections, we defined *HMGA2*-positive tumors as those tumors with at least moderate immunoreactivity for *HMGA2* (score ≥ 2).

In high-grade papillary serous carcinomas, we found 64% of tumors (18 out of 28) were moderately to strongly immunoreactive for *HMGA2* (Table 2). The immunopositive cells for *HMGA2* ranged from 40 to 100%. In contrast, only 10% serous borderline tumors (1 out of 10) were immunoreactive for *HMGA2* (Table 2 and Figure 1).

In carcinosarcoma, the rate of immunoreactivity for *HMGA2* was 60% of cases (9 out of 15) in carcinoma component and 47% (7 out of 15) in sarcoma (Table 2 and Figure 2). Most cases of carcinosarcoma contained carcinoma of serous differentiation. The similar rate of immunoreactivity for *HMGA2* in papillary serous carcinomas and carcinoma component of carcinosarcoma suggested a similar function of *HMGA2* in these two types of ovarian malignancies. Among 30 cases of endometrioid ovarian carcinomas, only 2 cases (7%) were immunoreactive for *HMGA2*. One of endometrioid ovarian carcinoma was strongly immunoreactive for both *HMGA2* and *p53* (Figure 1). Our findings indicated that endometrioid carcinoma of ovaries was mostly negative for *HMGA2*. About 23% of clear cell ovarian carcinomas (3 out of 13) were immunoreactive for *HMGA2*. Further study revealed that all three *HMGA2*-positive clear cell ovarian carcinomas had strong immunoreactivity for *p53* (Figures 1 and 3). Of 15 mucinous ovarian carcinomas, 1 (6%) was immunoreactive for *HMGA2*, which was the lowest rate of *HMGA2* overexpression in all ovarian carcinomas (Table 2 and Figure 3).

Statistical analysis indicated that the rate and levels of immunoreactivity for *HMGA2* were significantly higher in high-grade papillary serous carcinomas and carcinosarcomas than in other types of ovarian cancers ($P<0.05$) (Table 2).

HMGA1 and *p53* Expression in Different Types of Ovarian Cancer

High-mobility-group A1 gene (*HMGA1*) is one of the gene family members of *HMGA2*. *HMGA1* expression in ovarian cancer is largely unknown. We examined *HMGA1* expression in the serial sections of the same population of ovarian cancer. As in Table 2 and Figure 1, *HMGA1* is weakly and moderately immunoreactive for all types of ovarian cancer. The percentage of *HMGA1*-positive cases ranged from 82% for endometrioid carcinoma to 100% for clear cell carcinoma. The average levels of *HMGA1* ranged from 0.91 to 1.43 (Table 2). The levels and rates of immunoreactivity for *HMGA1*

Table 2 Differential expression of the selected markers in ovarian cancer

	No. of cases	*Immunointensity (mean ± s.e.m.)*			
		HMGA1	*HMGA2*	*p53*	*Ki-67*
HG-PSC	30	1.06 ± 0.11	1.57 ± 0.23	1.79 ± 0.26	38.46 ± 5.10
MMMT	15	1.43 ± 0.13	1.50 ± 0.31	2.00 ± 0.35	49.64 ± 5.36
SBT	10	1.43 ± 0.10	0.22 ± 0.21	0.44 ± 0.28	16.25 ± 5.81
EOC	30	0.91 ± 0.09	0.14 ± 0.10	0.75 ± 0.23	31.07 ± 5.39
MOC	15	1.07 ± 0.15	0.13 ± 0.13	0.27 ± 0.17	18.34 ± 5.67
CCOC	15	1.08 ± 0.08	0.54 ± 0.27	0.46 ± 0.23	27.69 ± 6.69
P-values	>0.05	<0.05	<0.05	>0.05	
		No. of immunopositivity (%)			
		HMGA1	*HMGA2*	*p53*[a]	
HG-PSC	30	24 (85.7)	18 (64.3)	18 (64.3)	
MMMT	15	15 (100)	9 (64.3)	10 (66.7)	
SBT	10	8 (88.9)	1 (10.0)	2 (20.0)	
EOC	30	23 (82.1)	2 (7.1)	8 (28.6)	
MOC	15	13 (86.7)	1 (6.7)	2 (13.3)	
CCOC	15	15 (100)	3 (23.1)	3 (23.1)	

CCOC: clear cell ovarian carcinoma; EOC: endometrioid ovarian carcinoma; HG-PSC: high-grade papillary serous carcinoma; MOC: mucinous ovarian carcinoma; MMMT: malignant mixed Mullerian tumor; SBT: serous borderline tumor.

[a]Score ≥ 2 was counted as immunopositive case.

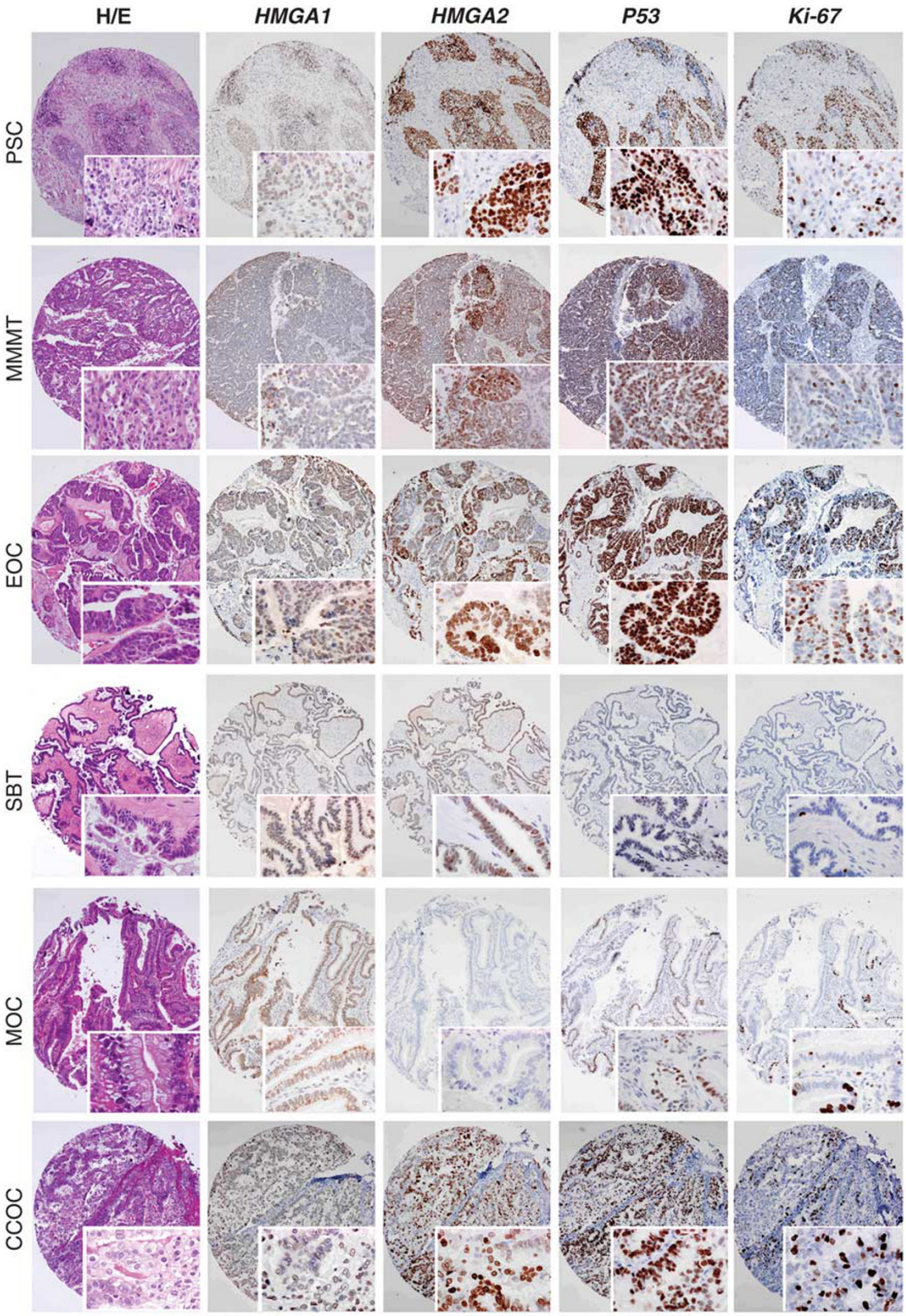

Figure 1 Photomicrographs illustrate examples of immunoreactivity for *HMGA1*, *HMGA2*, *p53* and *Ki-67* in six different histological types of ovarian cancer. Hematoxylin and eosin (H/E) and immunohistochemical stains for the selected markers were performed in serial sections of tissue core with low magnification ($\times 4$) and inset with high magnification ($\times 40$). PSC, high-grade serous papillary carcinoma; MMMT, carcinosarcoma; EOC, endometrioid ovarian carcinoma; SBT, serous borderline tumor; MOC, mucinous ovarian carcinoma; CCOC, clear cell ovarian carcinoma.

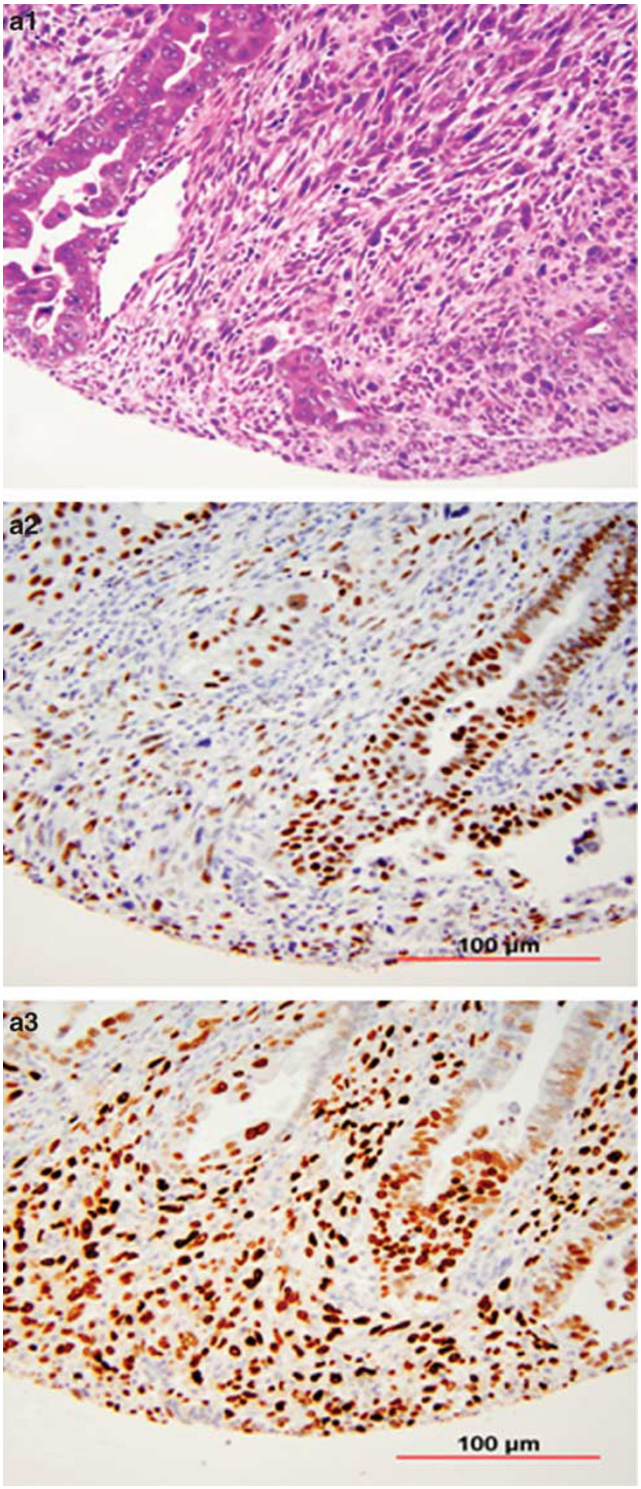

Figure 2 Photomicrographs illustrate immunoreactivity for *HMGA2* (**a2**) and *p53* (**a3**) in carcinosarcoma. Examples showed immunoreactivity for *HMGA2* and *p53* were present in both epithelial and stromal components. (**a1**) H/E stain.

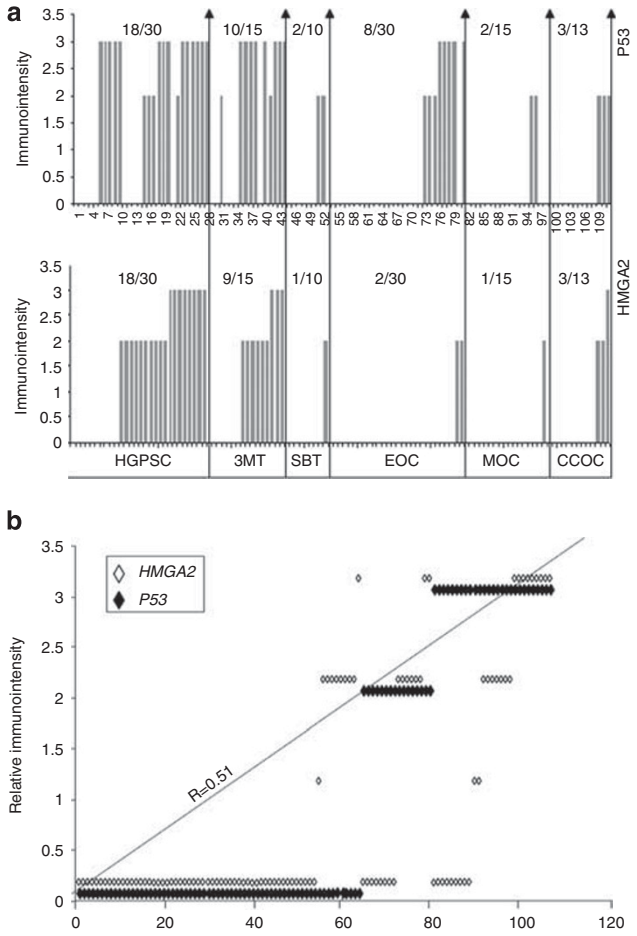

Figure 3 Immunoprofile analyses of *HMGA2* and *p53* in six different histological types of ovarian cancer. (**a**) Histogram (each gray bar representing one case) shows the relative levels (y axis, immunointensity) and rates (above histobars) of *HMGA2* (lower) and *p53* (upper) expression in six different types of ovarian cancer. The relative expression was sorted based on the *HMGA2* expression from negative to the highest levels. Arrow bars separate each tumor type (indicated at bottom). HGPSC, high-grade serous papillary carcinoma; MMMT, carcinosarcoma; EOC, endometrioid carcinoma; SBT, serous borderline tumor; MOC, mucinous ovarian carcinoma; CCOC, clear cell ovarian carcinoma. (**b**) Correlation analysis of *HMGA2* (red dots) with *p53* (blue dots) in 115 cases of ovarian cancer.

were statistically insignificant among different types of ovarian cancer ($P>0.05$). We further examined the expression of *p53* in the serial sections of all selected cases. We defined *p53*-positive cases as at least moderate and diffuse immunoreactivity for *p53*. We found that the rate of immunoreactivity for *p53* varied widely among different types of ovarian cancers. High-grade papillary serous carcinomas and carcinosarcomas had the highest rate of *p53* immunopositivity, 64% and 67%, respectively. All other types of ovarian cancers showed low rates of *p53* immunoreactivity ranging from 13 to 28% of cases (Table 2 and Figure 3). Statistical analysis indicated that *p53* was significantly higher in high-grade papillary serous carcinomas and carcinosarcomas than in other types of ovarian cancers (Table 2). In serial sections, we found that expression of *p53* was moderately correlated with *HMGA2* expression ($r=0.51$) as shown in Figure 3b.

The proliferation index (immunopositivity for *Ki-67*) in six different types of ovarian cancers varied widely. Overall, carcinosarcoma had the highest *Ki-67* index (50% positive cells), followed by high-grade papillary serous carcinoma (39%), endometrioid ovarian carcinoma (31%) and clear cell ovarian carcinoma (27%). Mucinous ovarian carcinoma and serous borderline tumor had the lowest index at 18 and 16%, respectively. By correlation analysis, there were weak correlations between *HMGA2* and *p53*, and *HMGA2* and *Ki-67* ($r=0.35$ and 0.21, respectively). The weak correlation of *HMGA2* with *Ki-67* was negatively contributed by endometrioid ovarian carcinoma, in which, only lower rate of *HMGA2* and higher rate of *Ki-67* were observed (Table 2).

let-7 Expression in High-Grade Papillary Serous Carcinomas and Endometrioid Ovarian Carcinomas

let-7s were found to be downregulated in ovarian cancer. To characterize which types of ovarian cancer had significant downregulation of *let-7s*, we selected two *let-7* family members, *let-7b* and *let-7c* for the study. In contrast to *HMGA2* that is only expressed in tumor cells, but not in normal counterpart, *let-7s* are expressed in both normal and tumor cells. Therefore, to determine the differential examination of microRNAs *let-7s*, matched normal controls have to be used. As shown in Materials and methods section, in ovarian cancer of high-grade papillary serous carcinoma and endometrioid ovarian carcinoma, the case-matched normal tissue controls from fallopian tube and endometrium were collected. We acknowledged that normal endometrium and fallopian tube might not be the best controls for ovarian high-grade papillary serous carcinomas and endometrioid ovarian carcinomas, but they were the closest one we could get. We examined *let-7b* and *let-7c* expression by microRNA *in situ* hybridization, along with *U6* as internal small RNA control.

We found that there was significant downregulation of *let-7b* in high-grade papillary serous carcinomas (1.04 ± 0.14) in comparison to matched fallopian tube epithelium (2.04 ± 0.10) ($P<0.05$) (Figure 4). Downregulation of *let-7c* had a similar pattern but less significant as *let-7c* had lower expression level in both normal fallopian tube epithelia (1.31 ± 0.11) and tumor cells (0.69 ± 0.13). No significant differences of *let-7* expression were noted between endometrioid ovarian carcinomas (*let-7b*, 1.35 ± 0.11; *let-7c*, 0.77 ± 0.16) and endometrium (*let-7b*, 1.45 ± 0.11; *let-7c*, 0.86 ± 0.12) (Figure 4).

Discussion

HMGA2 overexpression in ovarian cancer has been reported. Malek *et al*[7] found that over 65% of ovarian serous carcinoma were positive for *HMGA2*, whereas all normal ovarian epithelial lined tissues were negative for *HMGA2*.[7] Shell *et al*[16] examined *HMGA2* expression by immunohistochemistry in 100 primary ovarian cancer tissues (77% were serous type) and they found that high expression of *HMGA2* significantly correlated with an adverse prognosis.

Ovarian cancer is a group of heterogeneous diseases, involving different molecular pathways. To study the function of *HMGA2* in ovarian cancer, it is important to define which types of ovarian cancer are associated with *HMGA2* overexpression. Kurman and Shih[21] proposed a model for ovarian tumorigenesis. Ovarian tumors are divided into two groups designated as type I and type II. Type I tumors are slow growing, generally confined to the ovary at diagnosis and develop from well-established precursor lesions. Type I tumors include low-grade micropapillary serous, mucinous, endometrioid and clear cell carcinomas. They are genetically stable and are characterized by mutations in a number of different genes, including *KRAS*, *BRAF*, *PTEN* and β-catenin.[3,22,23]

Type II tumors are rapidly growing highly aggressive neoplasms for which precursor lesions arising from Fimbria are currently under intensive studies.[24] Type II tumors include high-grade serous carcinoma, carcinosarcoma and undifferentiated carcinoma. This group of tumors has a high level of genetic instability and is characterized by mutations of *p53*.[3] In this study, we found *HMGA2* overexpression was commonly seen in type II tumors, including high-grade papillary serous carcinoma and carcinosarcoma. In addition, we found that *HMGA2* overexpression is moderately correlated with *p53* expression (Figure 3). We propose that *HMGA2* overexpression is an important biomarker, in conjugated with *p53*, for the diagnosis and possibly associated with tumorigenesis of type II ovarian carcinoma.

In a recent study, we found that serous intraepithelial carcinoma in fallopian tube had high rate and level of *HMGA2* overexpression along with *p53*-dominant mutations.[20] The findings indicate that *HMGA2* overexpression is an early event in the tumorigenesis of high-grade papillary serous carcinoma. Further study by characterization of functional relationship between *p53* mutations and *HMGA2* overexpression will be valuable for understanding the functional task of *HMGA2* in the tumorigenesis of high-grade papillary serous carcinoma.

HMGA2 overexpression is present in many different epithelial and mesenchymal neoplasms. *HMGA2* in regulation of the molecular pathways responsible for tumorigenesis and tumor progression were only partially understood. In the study of 60 cancer cell lines, Peter's research group found that *HMGA2* is one of a few gene markers that can distinguish most type I (express mesenchymal gene signature) from

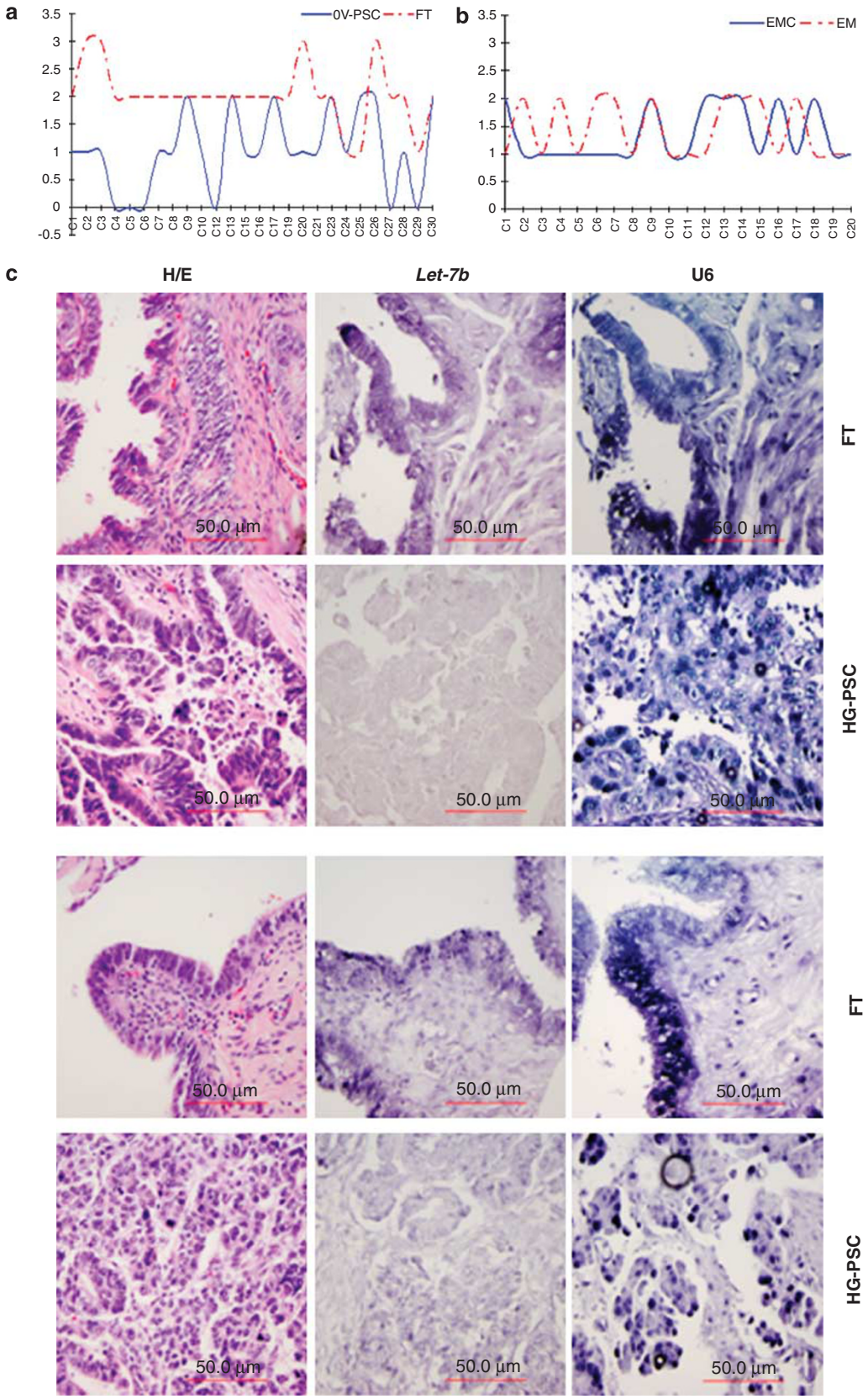

Figure 4 *let-7b* expression in high-grade papillary serous carcinomas (HG-PSC) and endometrioid ovarian carcinomas (EOC). (**a**) Relative expression of *let-7b* (y axis) in high-grade papillary serous carcinomas (red dot line) and matched fallopian tube epithelia (FT, blue solid line) in a total 30 cases. (**b**) Relative expression of *let-7b* (y axis) in endometrioid ovarian carcinomas (red dot line) and matched endometrium (EM, blue solid line) in a total 20 cases. (**c**) Photomicrographs illustrate some examples of intensity of *let-7b* expression in high-grade papillary serous carcinomas and FT. U6 is RNA quality control. The intensity of blue color indicates the levels of *let-7b* expression.

type II (express epithelial gene signature) cancer cell lines.[9,16] *HMGA2* participates in epithelial–mesenchymal transition,[25,26] a key step in tumor plasticity by converting adherent epithelial cells to motile mesenchymal cells[27] through the functional loss of E-cadherin, which is required to maintain epithelial cell–cell adhesion.[27] *HMGA2* overexpression is associated with tumor growth,[28] differentiation,[9,16,28] metastasis,[29] unfavorable outcome and resistance to treatment.[25,30] The function of *HMGA2* in behaviors of aggressive tumor growth in ovarian high-grade papillary serous carcinomas deserves further investigation.

Members of the *let-7* microRNA family function as tumor suppressors through specific repression of its target gene, particularly of *HMGA2* expression in some tumor cells both *in vivo* and *in vitro*.[17] The biological importance of molecular pairing of *let-7*::*HMGA2* has been shown by repression of *HMGA2* by *let-7s* which impairs tumor cell proliferation in many different tumor types.[14,15,17] To study whether overexpression of *HMGA2* is associated with loss of *let-7* expression, in this study, we examined two family members of *let-7*. We found that *let-7b* was significantly downregulated in high-grade papillary serous carcinoma against fallopian tube epithelia (Figure 4). We proposed that loss of *let-7s* can be part of pathogenesis in high-grade papillary serous carcinoma.

In conclusion, our study suggests that *HMGA2* overexpression is an important molecular change specifically related to high-grade papillary serous carcinomas. *HMGA2* overexpression is associated with *p53*-dominant mutations and *let-7* downregulation. In addition, *HMGA2* overexpression can be a potential biomarker in conjugation with *p53* for the detection and differentiation of ovarian high-grade papillary serous carcinomas.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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