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Original Article

Expression analysis of *URI/RMP* gene in endometrioid adenocarcinoma by tissue microarray immunohistochemistry

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Abstract: Multiple studies have recently demonstrated the oncogenic property of URI (or RMP, a member of the prefoldin family of molecular chaperones) during progression of hepatocellular carcinoma, ovarian cancer, and possibly prostate cancer. Most recently, we have shown that URI/RMP is up-regulated in cervical cancer, another reproductive system tumor beside ovarian and prostate cancers. To investigate if URI/RMP also plays a role in other reproductive system tumors, especially in endometrioid adenocarcinoma, we analyzed URI/RMP expression in a TMA (tissue microarray) containing tissues from 30 cases of endometrioid adenocarcinoma (which covers tumor tissues from Grade I through Grade III) and adjacent endometrium by immunohistochemistry (IHC) and densitometry analysis using image-pro plus 6.0 software. Our results showed that the mean density of URI/RMP expression in cancerous tissue is slightly higher than that of the adjacent endometrial tissue, though not statistically significant ($p>0.05$). There is no significant difference either between the mean density of Grade III cancerous tissue and that of Grade I and II cancers. Notably, we detected significantly higher signal intensity in cancerous tissue of all 7 Grade III cases than that of their adjacent endometrial tissue ($p<0.05$), suggesting a correlation of URI/RMP expression with the differentiation and pathological classification of endometrioid adenocarcinoma. Together, our results demonstrate the heterogeneous expression of URI/RMP in endometrioid adenocarcinoma. The higher level of URI/RMP expression in high-grade endometrioid adenocarcinomas compared to tissues of adjacent endometrium or gland suggests a diagnostic and possibly, a prognostic value of URI/RMP in endometrioid adenocarcinoma.

Keywords: URI/RMP, tissue microarray, immunohistochemistry, endometrioid adenocarcinoma

Introduction

As an evolutionally conserved gene, URI (unconventional prefoldin RPB5 interactor) or RMP (RPB5-mediating protein), has been shown to play essential roles in ubiquitination and transcription through interaction with the RNA polymerase II subunit RPB5 [1-3]. Recently, there is growing evidence which suggests an oncogenic or anti-apoptotic property of URI/RMP upon malignant transformation of multiple cancers or (cancer) cell lines [4-6]. We have previously shown that URI/RMP regulates cell apoptosis and is required for the proliferation of hepatocellular carcinoma (HCC) [5]. URI was recently demonstrated to be overexpressed both in ovarian cancer cell lines and in ovarian carcinomas [6]. URI/RMP has also been shown to be essential for androgen receptor signaling, a pathway involving prostate cancer progression [7]. Most recently, we have shown that URI/RMP is up-regulated in cervical cancer [6]. This is intriguing, as cervical, ovarian, and prostate cancers are all reproductive system tumors. As another class of reproductive system tumors, endometrial cancers are the most common gynecologic cancers in developed countries affecting more than 142,200 newly diagnosed women each year [9, 10]. We therefore aim to explore the correlation of URI/RMP expression with endometrial cancer, here in, endometrioid adenocarcinoma, by TMA and IHC approaches,

Table 1. Information of tissues from 30 cases of endometrioid adenocarcinoma patients

Case group	Sex	Average age	Tissue type	Tissue origin	Tumor pathology
1) Grade I (3 cases)	F	60	Uterus carcinoma	Endometrioid adenocarcinoma	Poorly distributed gland, minimal invasion of the uterine wall (myometrium), mild nuclear atypia
			Adjacent tissue	Endometria	
2) Grade II (17 cases)	F	62.5	Uterus carcinoma	Endometrioid adenocarcinoma	A combination of glands, solid masses of epithelium, moderate nuclear atypia
			Adjacent tissue	Endometria	
3) Grade II-III (3 cases)	F	53	Uterus carcinoma	Endometrioid adenocarcinoma	Between grade II and grade III
			Adjacent tissue	Endometria	
4) Grade III (7 cases)	F	56	Uterus carcinoma	Endometrioid adenocarcinoma	Predominantly solid growth of tumor, deep invasion of myometrium, and severe nuclear atypia
			Adjacent tissue	Endometria	

so as to provide novel insight into the role of URI/RMP upon endometria carcinogenesis.

Materials and methods

RMP antibody and endometrioid adenocarcinoma TMA

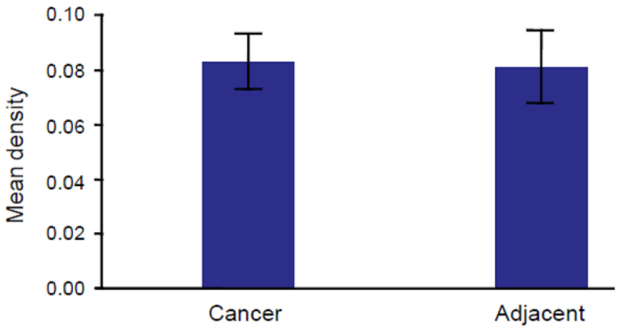
The URI/RMP polyclonal antibody (K-17, sc-103869) was purchased from Santa Cruz (CA USA). The immunoassay and detection kits poly-HRP anti-Goat IgG (PV-9003) and 3′-diaminobenzidene (DAB kit, ZLI-9032) are commercially available at Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd. The tissue microarray (TMA, OD-CT-RpUtr03-002) was purchased from Shanghai Outdo Biotech Co., Ltd (Shanghai, China). This TMA was prepared by dot-arraying tissues in parallel from 31 cases of endometrioid adenocarcinoma and adjacent endometrium. Due to drop of tissue in one case, we actually analyzed 30 cases of arrayed tissues from endometrioid adenocarcinoma patients. The pathological classification of these tumor tissues spread from Grade I through Grade III. Specifically, among the 30 cases analyzed, 3, 17, 3, and 7 cases are from Grade I, Grade II, Grade II-III, and Grade III endometrioid adenocarcinoma respectively. Detailed information of the arrayed tumor and adjacent endometrium is described in the result section.

Immunohistochemistry (IHC) assay

Immunohistochemical staining using RMP antibody (K-17, sc-103869, Santa Cruz, CA USA) was performed on arrayed tissue samples according to protocol as previously described [8]. Pre-experiment using extra sample slide was conducted to optimize the concentration of RMP antibody to be used in following IHC assay. Briefly, the TMA slides were incubated at an oven at 60°C for 20 minutes. After routine deparaffinization and rehydration, slides were pretreated with 10 mM sodium citrate buffer (pH 6.0) and boiled for 10 minutes for antigen retrieval. The endogenous peroxidase was quenched by adding the hydrogen peroxide (3% H_2O_2 in 100% ethanol) at room temperature for 15 minutes. After washing with PBS, the slides were blocked by non-immune rabbit serum in a wet box and incubated for 1o minutes. The blocking buffer was removed and the slides were then incubated overnight with primary RMP antibody at optimized concentration (1:100 dilutions) at 4°C. Slides were washed with the 1xTBST (Tris Buffered Saline with 0.1% Tween-20) solution and further incubated with poly-HRP anti-Goat IgG (PV-9003, Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.) for 15 minutes. Detection was using the 3, 3′-diaminobenzidene as instructed (DAB kit, ZLI-9032, Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.). Slides were counterstained with hematoxylin before microscopic analysis.

Microscope and image analysis

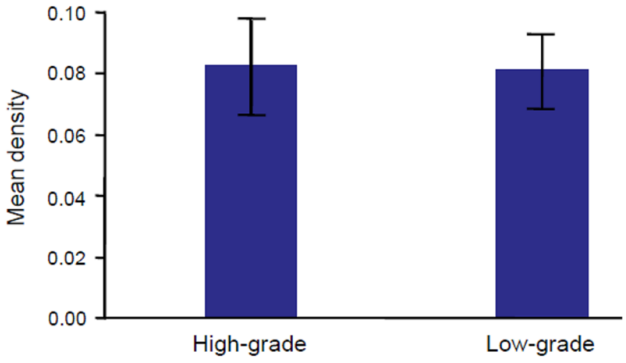
The URI/RMP expression in TMA of cancerous and adjacent tissues was subjected to microscopic analysis. Briefly, after IHC staining, if a cell or tissue was stained from light yellow to brown, it would be recorded as positive immunostaining. The areas from both cancer and its adjacent normal tissue were selected for analysis. Specifically, for the tumor tissue, cancerous



Groups	Cases	Mean density	Std error
Endometrial cancer	30	0.0823	0.0100
Adjacent endometria	30	0.0805	0.0131

P > 0.05

Figure 1. URI/RMP Expression in Cancerous and Adjacent Tissues. The mean density of cancerous and adjacent endometrial tissues from all 30 cases is illustrated at top graph and summarized in the table below. No statistically significant difference was detected between the mean density of cancerous tissues (0.0823±0.0100) and that of adjacent tissue (0.0805±0.0131), p>0.05.



Groups	Cases	Mean density	Std error
High-grade (II-III and III)	10	0.0832	0.0161
Low-grade (I and II)	20	0.0819	0.0130

P > 0.05

Figure 2. URI/RMP Expression in High-and Low-grade Endometrial Cancers. The mean density of cancerous tissues from 10 high-grade (Grade II-III and Grade III) and 20 low grade (Grade I and II) cases is illustrated at top graph and summarized in the table below. No statistically significant difference was detected between the mean density of cancerous tissues from high-grade cases (0.0832±0.0161) and that of low-grade cases (0.0819±0.0130), p>0.05.

gland or solid tumor area was selected, while for the adjacent tissue, normal endometrium and benign gland were selected. The intensity of the staining signal was measured and documented using the Image-Pro Plus 6.0 image analysis software (Media Cybernetics, Inc. Silver Spring, MD USA). The mean densitometry of the digital image (×400) is designated as representative URI/RMP staining intensity (indicating relative URI/RMP expression level). The signal density of tissue areas from five randomly selected visions were counted blindly and subjected for statistical analysis.

Statistical analysis

One-way ANOVA (SPSS16.0) was used to assess the significance of URI/RMP staining intensity across sample groups of endometrioid adenocarcinoma. Values (scores or signal intensities) are presented as means±SEM (standard error of mean). Paired t-test was used to compare the mean density of cancer and adjacent tissues. $p<0.05$ was considered statistically significant.

Results

Pathological distribution of the endometrial cancer TMA

The TMA used in this study contains arrayed tissues from 30 cases of endometrioid adenocarcinoma and their adjacent endometrium. The first 3 cases are pathologically classified as Grade I endometrioid adenocarcinoma. They are from 3 females (F) at the age of 53, 62, and 64 respectively. The tumors are either within the endometrium or show minimal invasion (less than 1/2) into the myometrium. There are 17 cases of Grade II endometrioid adenocarcinomas that are from females at the age ranging from 36 to 88 (average 62.5). The tumors of this group show a variety of phenotypes, including thickening of the endometrium, invasion into the myometrium (less or more than 1/2). The Grade II-III endometrioid adenocarcinomas were from 3 females at the age of 49, 53, and 57 respectively. The tumors of this group were defined based on their irregular tumor mass (tubular, diffusive, cancerous, and mushroom-like) and invasion into the myometrium. Finally, the 7 cases of Grade III endometrioid adenocarcinomas that are from females at the age ranging from 34 to 67 (average 56) showed character-

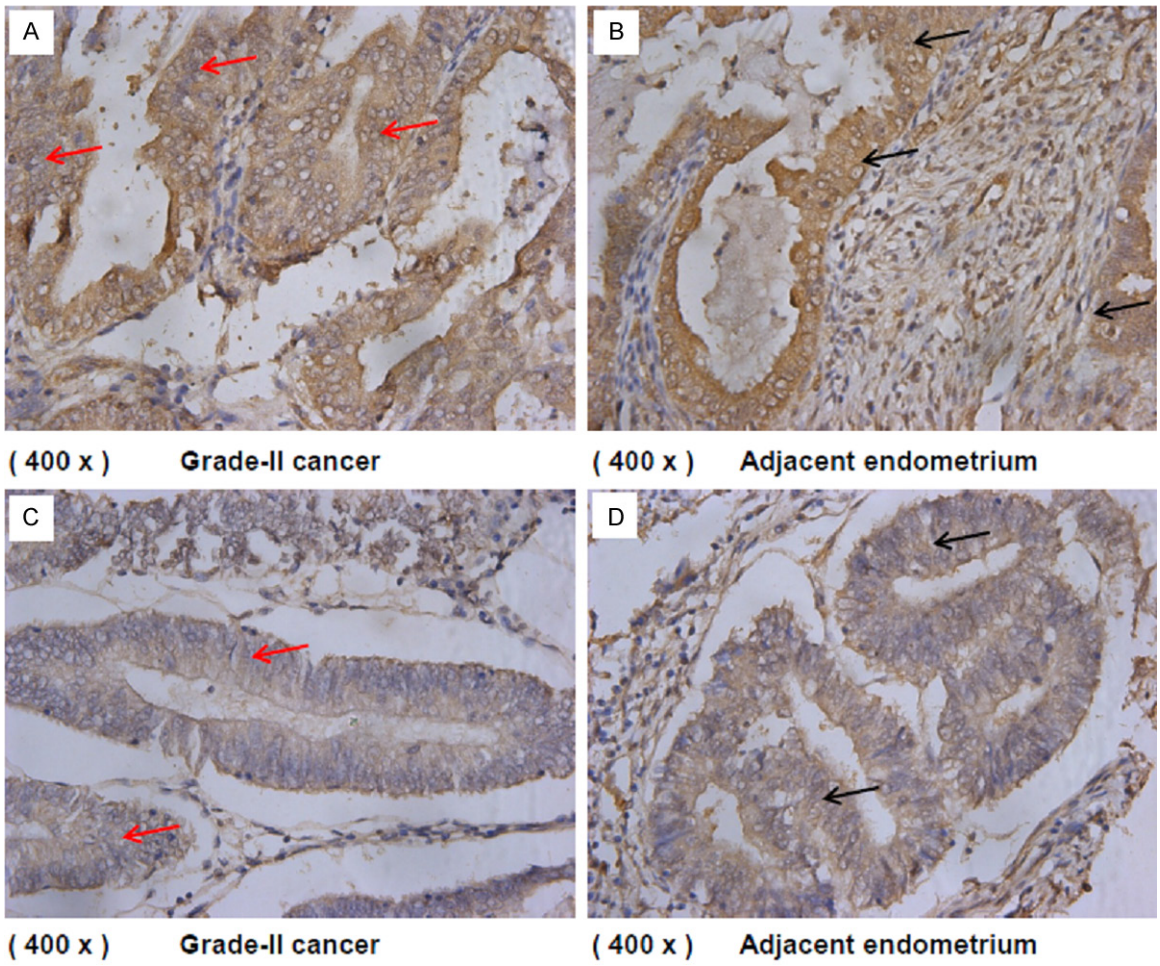


Figure 3. URI/RMP IHC in Representative Grade-II and Adjacent Endometria. Illustrated are tissue sections (400x) from representative endometrioid adenocarcinoma (Grade-II) case 1 (a 40 years old female, top panels A and B) and case 2 (a 41 years old female, bottom panels C and D). The immunostaining intensity (brown staining signal) between the cancerous (A, C) and their corresponding adjacent (B, D) tissues showed no difference, although heterogeneous staining were observed in cancerous and adjacent endometrium (or glands with dysplastic changes) among different cases.

istics of invasive endometrial cancer, including deep invasion of myometrium (more than 1/2), very irregular tumor mass (ulcerous or cauliflower-like clumps). Detailed information of the arrayed tumor and adjacent endometrium is summarized in **Table 1**.

URI/RMP expression in cancerous and adjacent tissues

To investigate the overall URI/RMP expression in endometrioid adenocarcinoma and its adjacent tissues, we performed IHC analysis using RMP antibody (K-17, sc-103869) and measured the density of the staining signal of all 30 cases using the Image-Pro Plus 6.0 image analysis software (Media Cybernetics, Inc. Silver Spring, MD USA). The mean density of cancerous tissues from all 30 cases is 0.0823±0.0100, while that of adjacent tissue is 0.0805±0.0131. The result suggests a slightly higher level of URI/RMP expression in cancerous tissues compared to their adjacent normal tissues, although no statistically significant difference was detected between the mean density of these two groups of tissues ($p>0.05$, **Figure 1**).

URI/RMP expression in high and low-grade endometrial cancers

To examine the potential correlation of URI/RMP expression with pathological classification of endometrioid adenocarcinoma, we calculated the staining intensity of high-grade (cases of

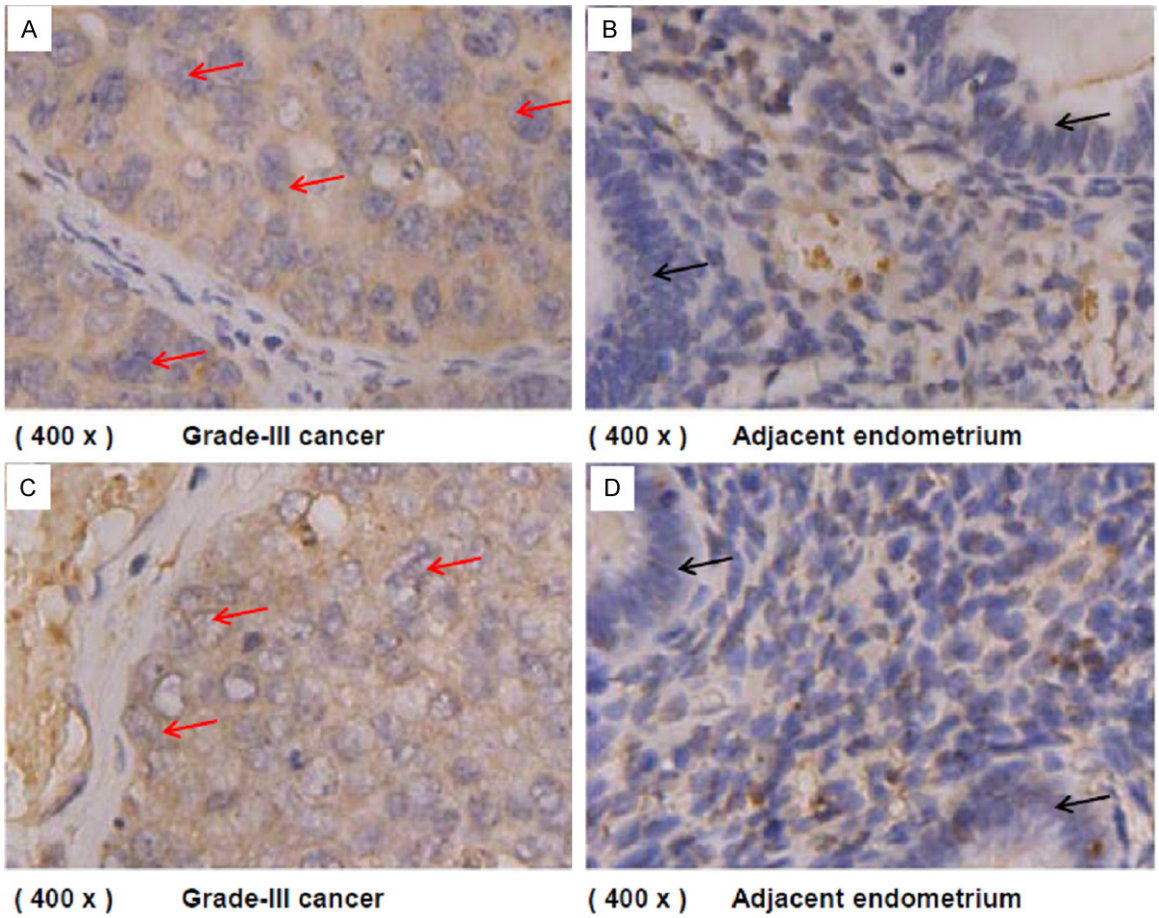


Figure 4. URI/RMP IHC in Representative Grade III and Adjacent Endometria. Illustrated are data from representative endometrioid adenocarcinoma (Grade-III) case 1 (a 46 years old female, top panels A and B) and case 2 (a 67 years old female, bottom panels C and D). Much stronger staining signal was shown in the solid tumor section areas (**Figure 4A** and **4C**) compared to that of their corresponding adjacent endometrium (**Figure 4B** and **4D**).

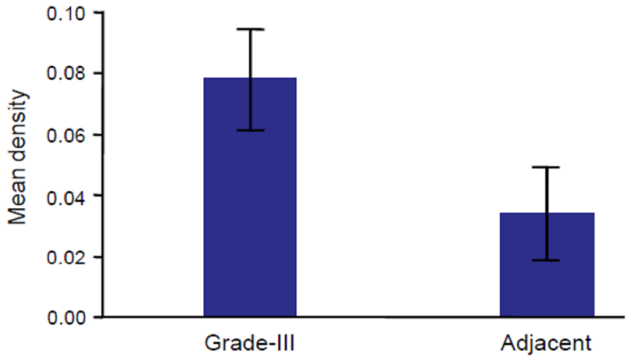
Grade II-III and Grade-III) tumor tissues and compared to that of low-grade tissues (cases of Grade-I and II). The mean density of cancerous tissues from Grade II-III and Grade III cases is 0.0832±0.0161, n=10, while the density of Grade I and II cases is 0.0819±0.0130, n=20. Although the mean density of high-grade cancers is slightly higher (suggesting higher-level URI/RMP expression) than that of low-grade cancers, the difference, however, is not statistically significant ($p>0.05$, **Figure 2**).

URI/RMP expression in low-grade cancer and adjacent tissues

To determine if URI/RMP expression is correlated with early stage endometrioid adenocarcinoma, we further compared the staining intensity of URI/RMP in low-grade (cases of Grade I and II) tumor tissues and their adjacent tissues. We did not detect statistically significant difference between the mean density of tumor tissue and that of adjacent tissue (data not shown). Given the limited number of Grade-I cases, the immunostaining of endometrioid adenocarcinoma and adjacent endometrium from two representative Grade-II cases is illustrated: no significant staining difference was observed between the cancerous (**Figure 3A** and **3C**) and their corresponding adjacent (**Figure 3B** and **3D**) tissues. However, differential staining intensity was observed among different Grade-II cases, suggesting heterogeneous URI/RMP expression in low-grade endometrial cancer patients.

URI/RMP expression in grade-III cancer and adjacent tissues

To determine if URI/RMP is upregulated during late stage of endometrioid adenocarcinoma progression, we specifically examined the stain-



Groups	Cases	Mean density	Std error
Grade III (only) cancer	7	0.0788	0.0170
Adjacent endometria	7	0.0345	0.0156

$P < 0.05$

Figure 5. URI/RMP in Grade III Tumors and Adjacent Endometria. The mean density of cancerous and adjacent endometrial tissues from 7 Grade III cases is illustrated at top graph and summarized in the table below. There is statistically significant difference between the mean density of Grade III tumors (0.0788±0.0170) and that of adjacent tissue (0.0345±0.0156), $p<0.05$.

ing intensity of Grade III tumor tissues and compared to their adjacent tissues. The IHC assay results showed that much stronger (brown) immunostaining was detected in tumor tissues of all 7 Grade-III cases compared to their adjacent tissues. Illustrated are data from two representative Grade-III cases: strong staining signal can be observed in the solid tumor section areas (**Figure 4A** and **4C**), while the corresponding adjacent endometrium (**Figure 4B** and **4D**) only show weak staining. We also calculated the mean density of cancerous and adjacent tissues. The result showed that the mean density of Grade III tumors (0.0788±0.0170, n=7) is significantly higher than that of adjacent tissues (0.0345±0.0156, n=7; $p<0.05$, **Figure 5**). This result suggests that URI/RMP is significantly upregulated in tissues of Grade III endometrioid adenocarcinoma compared to their adjacent endometria.

Discussion

URI/RMP is a multifunctional protein known to be involved in mTOR (mammalian target of rapamycin) signaling pathway [2, 11], regulation of transcriptional initiation [12], apoptosis, maintaining DNA stability, and DNA damage response [11, 13, 14]. These activities suggest a possible role of URI/RMP upon tumorigenesis. Indeed, previous studies have shown that URI/RMP is essential for liver cancer cell survival by promoting tumor cell proliferation and regulating cell cycle and apoptosis [5]. Interestingly, multiple recent studies have demonstrated the involvement of URI/RMP upon oncogenesis of reproductive system tumors, including ovarian, prostate, and cervical cancers [6-8]. This directly leads our attention to endometrial cancers, another group of reproductive system tumors.

Endometrial cancer is one of the most common invasive gynecologic malignancies in developed countries. It is also the third leading female cancer (behind ovarian and cervical cancers) that causes cancer death in women [15]. Given its close correlation with gynecologic cancers, we proceed to analyze URI/RMP expression in endometrial adenocarcinoma, the most common subtype of endometrial cancer, typically occurs within a few decades of menopause. Histologically, endometrial adenocarcinoma is classified as grade I through grade III based on the solid growth area of the tumor and the degree of nuclear atypia [16, 17]. The high-grade (Grade-III) tumors, which are characterized by poorly differentiated or fused cells with obvious nuclear atypia and barely recognizable glands, usually have poorer prognosis compared to the low-grade (Grade I and II) tumors. While it is not clear what causes most cases of endometrial adenocarcinoma, there are certain risk factors, including obesity and hormone imbalance (interactions between estrogen and/or progesterone receptors with their hormones), that may contribute to its tumor growth [15, 18]. Interestingly, previous studies have suggested the role of URI/RMP in prostate cancer progression due to its involvement in androgen receptor signaling pathway [7]. We examined URI/RMP expression in arrayed tumor and adjacent tissues derived from 30 cases of endometrioid adenocarcinoma patients. We detected a varied level of URI/RMP expression both in tumor and in adjacent tissues. Although the overall URI/RMP expression in tumor tissues is slightly higher than that of adjacent endometria, the URI/RMP level in high-grade (Grade II-III and Grade III) tumors is also slightly higher than that of low-grade (Grade I and II) tumors, the

difference, however, is not statistically significant.

We further compared URI/RMP expression in tumor and adjacent tissues of low-grade (Grade I and II) tumors. We did not observe significant staining difference between the cancerous and their adjacent tissues, suggesting insignificant role of URI/RMP in development of early stage endometrioid adenocarcinoma. We also observed heterogeneous URI/RMP expression both in tumor and in adjacent tissues of these low-grade tumors. This is partly due to the uncertainty of selection and grading of some of the tumor tissues. It may also be due to the limitation of selected adjacent tissues, as some of the tumor tissues lack normal gland but glands with pre-cancerous dysplastic changes, which may show relatively high level of URI/RMP expression (**Figure 3**). Notably, we have compared the immunostaining intensity of URI/RMP in tumor and adjacent tissues of high-grade (Grade III) tumors, significantly higher staining intensity indicating upregulated URI/RMP expression was observed in all 7 cases of grade III tumors compared to their adjacent endometria. This suggests that the expression level of URI/RMP may be linked to differentiation, grading, and especially the late-stage development of endometrial adenocarcinoma.

Whether URI/RMP is a biomarker of endometrial cancer, or correlates with its prognosis remains to be determined. Previous studies have demonstrated that multiple factors, including the stage of disease, histological grade and type of carcinoma, depth of myometrial invasion, lymph node status, as well as lymphovascular and cervical involvement, influence the prognosis of endometrial cancer [19]. The upregulated URI/RMP expression in late-stage tumors may indicate its poor prognosis. Meanwhile, beside surgery, the most common treatment for endometrial cancer, chemotherapy and hormone replacement are important treatment choice for high-risk and recurrent endometrial cancers [20]. However, chemoresistance (such as cisplatin-resistance), which is due to anti-apoptosis of tumor cells, is not uncommon in endometrial cancer and usually leads to poor prognosis or survival [20]. The mammalian target of rapamycin inhibitors, and possibly tyrosine kinase or angiogenesis inhibitors, represent rather novel agents that have the potential to treat advanced endometrial cancers [21]. Notably, previous studies have indicated the close correlation of URI/RMP with mTOR signaling in mammalian cells [2, 13]. Moreover, URI has been shown to be amplified in ovarian cancer and promote its cancer cell survival by affecting PI3K-mTOR signaling pathway. URI amplification mediates increased resistance to rapamycin, while depletion of URI enhanced the sensitivity of ovarian cancer cells to cisplatin [6]. These lines of evidence highlight the importance to further investigate the mechanism and clinical relevance of high-level URI/RMP expression in endometrial cancer.

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Disclosure of conflict of interest

All authors have no conflict of Interest.

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