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Peer Reviewer of *World Journal of Clinical Cases*, Ralph Victor Yap, MD, RN, Assistant Professor, Surgeon, Department of Surgery, Cebu Doctors' University Hospital, Cebu 6000, Philippines. rvyapmd@gmail.com

## AIMS AND SCOPE

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EDITORIAL

# Paired box proteins as diagnostic biomarkers for endocervical adenocarcinoma

Jia-Hui Zhou, Xiang-Ning Zhang

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**Jia-Hui Zhou**, Pathology Department, Lishui Central Hospital, Lishui 323000, Zhejiang Province, China

**Xiang-Ning Zhang**, Pathophysiology Department, Guangdong Medical University, Dongguan 523808, Guangdong Province, China

**Corresponding author:** Xiang-Ning Zhang, MD, PhD, Associate Professor, Pathophysiology Department, Guangdong Medical university, No. 1 Xincheng Avenue, Songshan Lake Scientific and Industrial Park, Dongguan 523808, Guangdong Province, China.
zhangxn_2006@126.com

## Abstract

In this editorial, we commented on the article by Akers *et al* published in the recent issue of the *World Journal of Clinical Cases*. We focused specifically on the role of the transcription factor paired box protein 8 (PAX8) belonging to the family PAX in the carcinogenesis of a gynecologic tumor, endocervical adenocarcinoma, arising from the tissue of mesonephric origin, and the potential diagnostic value for the same type of neoplasms. The global vaccination program of human papillomavirus (HPV) has dramatically reduced the incidence of cervical cancer, including cases of adenocarcinoma. The type of adenoid epithelial origin has a lower frequency of HPV detection but tends to be more aggressive and fatal. Cases of endocervical adenocarcinoma occurring in females of menopause age have been described in the 2023 volume of the *World Journal of Clinical Cases* and in our study recently published in *Oncol Lett*. The histopathological findings and immunohistochemical assays showed that the lesions had glandular morphology, and the specimens in these two reports were immunohistochemically positive for the transcription factor PAX8, albeit that they had opposing expression profiles of tumor suppressor p16 and estrogen receptor and the presence of the HPV genome. The presence of a mucin protein, MUC 5AC, as revealed in both studies suggested target molecules for the diagnosis of mucinous adenoid type of uterine tumor and other histological origins. The clinical outcome was unfavorable due to metastasis and recurrence. This prompted the improvement of the antitumor modality, with the introduction of precise targeting therapy. Mucin has now been reported to be the therapeutic target for adenocarcinomas.

**Key Words:** Cervical adenocarcinoma; Diagnostic biomarker; Paired box protein 8; Embryogenesis; Transcription factor

**Core Tip:** Paired box proteins (PAXs) are a family of transcription factors that play an important role in the embryogenesis of different tissues through the regulation of gene expression. PAX 2, 5, and 8 are expressed in the sites of mesonephric tissues, and their deregulation contributes to the genesis of urogenital tumors such as cervical and ovarian cancers. Immunohistochemical staining and in situ hybridization tests revealed that the specimens of endocervical adenocarcinoma were positive for the transcription factor PAX8 and human papillomavirus. It is proposed that combined with mucin of glandular tumor, PAX8 can be used as a diagnostic marker for cervical adenocarcinoma.

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## INTRODUCTION

In 2023, a report by Akers *et al*[1] published in the *World Journal of Clinical Cases* described a case of distant metastasis of cervical adenocarcinoma with alterations in several biomarkers including tumor suppressor p16, estrogen receptor, and transcription factor paired box protein 8 (PAX8). The case was also positive for human papillomavirus (HPV)[1]. We recently reported 2 cases of gastric-type endocervical adenocarcinoma; one of the patients was immunohistochemically positive for PAX8[2]. Because PAX protein expression related to the tissue origin of lesions during embryogenesis and published data on the involvement of PAX proteins in the cancers of the ovary and uterine cervix, we aimed to dissect the possible significance of using PAX proteins, especially PAX8, as diagnostic and therapeutic targets of cervical adenocarcinoma.

### Role of PAX proteins in mesonephric embryogenesis and carcinogenesis

Gynecologic tumors such as ovarian and cervical cancers arise from the tissues of mesonephric origin during embryogenesis. The transcription factors regulate embryonic development and play a role in organogenesis. The aberrant expression is responsible for the genesis of malignancies. Some members of the PAX family are implicated in these processes.

The PAX family comprises nine members, namely PAX1-9. They are divided into four groups based on their distinct molecular motif composition. The transcription factors are preferentially expressed in different anatomic sites during human embryogenesis to regulate gene expression; in relation to this, the PAX protein family molecules also contribute to carcinogenesis in specific parts of the body.

The members of the PAX family preferentially contribute to the regulation of gene expression of different organs; early expression of PAX2 is essential for the formation of the mesonephric duct[3]. It also compensates for the reduced expression of PAX8 throughout kidney development; the expression of PAX8 is activated in kidney and thyroid tissue during their organogenesis process[4]. In addition, PAX1 and PAX9 are implicated in the development of the skeleton. PAX2, 3, 5, 6, 7, and 8 are implicated in the development of the central nervous system[5], and aberrant expression of these PAX family members contributes to malignancies of the kidneys, thyroid gland, ovary, fallopian tube, and uterine cervix[6-8]. Table 1 summarizes the biological classification and activities of PAX family proteins including their role in tumorigenicity.

### Role of PAX proteins in the genesis of cervical adenocarcinoma

Two major types of tumors, squamous carcinoma and adenocarcinoma[9,10], arise in the epithelial lining of the uterine cervix. Cervical cancer predominantly of squamous epithelial origin is associated with infection of high-risk HPV like types 16 and 18. The high incidence of HPV infection in cell cervical carcinoma offers an opportunity for global eradication through HPV vaccination[11]. Cervical adenocarcinomas, however, form a spectrum from well-differentiated adenoma malignum (a mucinous variant of minimal deviation adenocarcinoma) to poorly differentiated, invasive gastric-type adenocarcinoma[12,13]. Endocervical carcinoma, specifically gastric-type cervical adenocarcinoma, has a low incidence of HPV infection.

Generally, adenocarcinoma of the cervix has a poor prognosis. Regarding distant metastasis, cervical cancer typically metastasizes to local structures through direct invasion, hematogenous dissemination, or dissemination through the lymphatic system[14,15]. It was reported that breast metastases of cervical cancer occurred in the case of high-grade adenocarcinoma with mucinous features that we discussed in our case study[2].

**Table 1 Classification, embryogenesis, and tumorigenicity of paired box protein family proteins**

| Group in PAX family | Member in PAX family | Expression site during embryogenesis | Involvement in tumorigenicity |
|---|---|---|---|
| I | PAX1 | Skeleton, thymus, pharyngeal pouch | |
| | PAX9 | Skeleton, teeth, thymus | |
| | PAX2 | Kidney, CNS | Bladder and renal cancers |
| II | PAX5 | B cells, CNS | Lymphomas |
| | PAX8 | Kidneys, thyroid gland, CNS | Thyroid, ovarian, and cervical cancers |
| III | PAX3 | Neural crest, CNS, muscle | Melanoma, rhabdomyosarcoma |
| | PAX7 | Same as above | Rhabdomyosarcoma |
| IV | PAX4 | Pancreas, gut | |
| | PAX5 | Pancreas, gut, and eyes | Gastrointestinal cancers |

CNS: Central nervous system; PAX: Paired box protein.

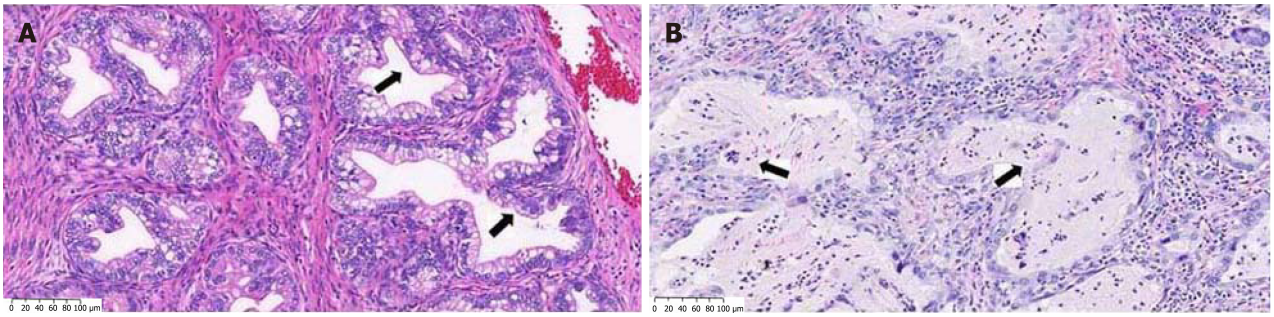


**Figure 1 Histopathologic presentation of endocervical adenocarcinoma.** Representative microscopic images of 2 cases of gastric-type endocervical adenocarcinoma. A: Case 1; B: Case 2. The scale bar is a length of 100 μm.

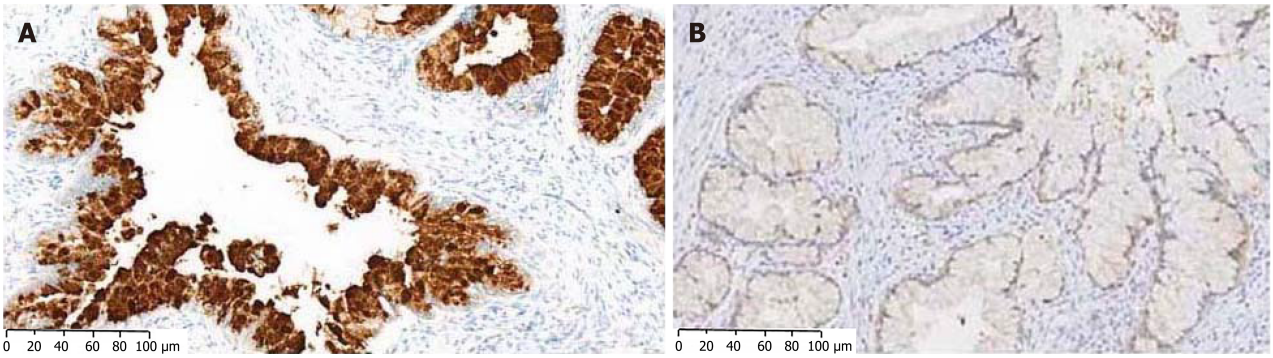


**Figure 2 Immunohistochemical staining of gastric endocervical adenocarcinoma.** A: Positive staining for a mucin protein, MUC 5AC, which is a biomarker of mucinous glandular tumor of the uterine cervix; B: Positive staining for the transcription factor paired box protein 8. The scale bar represents a length of 100 μm.

In situ hybridization test revealed that the case of cervical adenocarcinoma was positive for HPV and the transcription factor PAX8. Similarly, we reported 2 cases of gastric-type endocervical adenocarcinoma with one case being positive for PAX8[2]. Our cases presented as lesions of glandular appearance, and microscopically the tumor cells presented as cells of adenoid epithelium (Figure 1). In addition to PAX8 they were positive for a mucin protein, MUC 5AC (Figure 2), and negative for HPV. Furthermore, in contrast to the present report, our cases were negative for both estrogen receptor and the tumor suppressor p16.

Both PAX2 and PAX8 play an important role in the genesis of the anatomic structure of the ovary, uterus cervix, and uterus corpus during embryonic development. It has been shown that PAX8 is expressed in tumors of the thyroid gland, kidneys, and Müllerian tube, such as malignancies of ovary and endometrium, and its incidence of detection is high in ovarian cancer[16-20]. The possible involvement of PAX8 has been revealed in the genesis of cervical cancer[21,22].

PAX 8 has been recognized as a DNA binding transcription factor. A binding site for it has been identified in the promoter region in Wilms' tumor gene (*WT1*), coding for a product for the development of kidney and gonadal glands. The data suggested that part of its role in kidney development was as a modulator of WT1 expression in the kidney[23]. It remains to be tested whether tumors of the cervix and ovary have altered expression of WT1. While high PAX8 level is present in thyroid cancers, it has been reported that the coding region of *PAX8* is mutated in patients of thyroid dysgenesis, and it is responsible for elevated thyroid-stimulating hormone levels in congenital hypothyroidism[24]. Given this, the molecules of particular members of the PAX family are proposed to be indicators or biomarkers for the diagnosis of cervical adenocarcinoma or cancer of the cervix in general.

The expression of PAX8 has been noted in tumors of thyroid, renal, and Müllerian tube origins, like neoplasms originating from ovary and endometrium. Meanwhile, however, PAX8 was reported to be expressed in all 20 cases (100%) of benign endocervical epithelium specimens. Additionally, it was expressed in 97%-100% of adenocarcinoma in situ and in 0%-87% of endocervical adenocarcinoma specimens[25,26]. These findings suggest that the incidence of PAX proteins is low with the progression of the tumor and that the aberrant expression profile of tissue antigen due to the differentiation status in malignancy may account for negative PAX8 expression in 1 of our reported cases. The study of numerous clinical samples is needed to clarify this issue.

## CONCLUSION

Multiple drivers of cancer involve the genesis of cervical cancer. We immunohistochemically detected the presence of mutant p53 in our reports. However, the oncogenicity-related changes could be highly heterogeneous; our study revealed the absence of mutant *k-ras* as assayed using a PCR-based amplification refractory mutant system[2]. Our early work showed that in HPV-positive cervical cancer cases, oncogene *c-myc* was overexpressed due to exon alteration[27] and the change in c-myc, which cooperates with mutant k-ras, results in malignancy, as reported in another study[28]. The gain-of-function mutations of oncogenes together with the mutation of tumor suppressor genes are common changes in malignancies but less specific to particular neoplasms of certain histologic origins. It is therefore proposed that molecules implicated in organogenesis related to tumors can be used as therapeutic targets for adenocarcinomas. The PAX family proteins may fulfill such demands[29,30].

## FOOTNOTES

**Author contributions:** Zhou JH and Zhang XN conceived the idea and performed the study; Zhou JH prepared the primary draft, figures, and table; Zhang XN corrected the manuscript and revised the figures and table; Both authors read and approved the final version of the paper and agreed on its submission.

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**Country of origin:** China

**ORCID number:** Jia-Hui Zhou 0000-0002-9735-685x; Xiang-Ning Zhang 0000-0002-7875-5548.

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## REFERENCES

1 **Akers A**, Read S, Feldman J, Gooden C, English DP. Diagnostic challenges and individualized treatment of cervical adenocarcinoma metastases to the breast: A case report. *World J Clin Cases* 2024; **12**: 412-417 [PMID: 38313645 DOI: 10.12998/wjcc.v12.i2.412]
2 **Zhou J**, Zhang X, Mao W, Zhu Y, Yan L, Jiang J, Zhang M. Pathological features of gastric-type endocervical adenocarcinoma: A report of two cases. *Oncol Lett* 2024; **27**: 149 [PMID: 38406594 DOI: 10.3892/ol.2024.14282]
3 **Dressler GR**, Wilkinson JE, Rothenpieler UW, Patterson LT, Williams-Simons L, Westphal H. Deregulation of Pax-2 expression in transgenic mice generates severe kidney abnormalities. *Nature* 1993; **362**: 65-67 [PMID: 8383297 DOI: 10.1038/362065a0]
4 **Mansouri A**, Chowdhury K, Gruss P. Follicular cells of the thyroid gland require Pax8 gene function. *Nat Genet* 1998; **19**: 87-90 [PMID: 9590297 DOI: 10.1038/ng0598-87]
5 **Lang D**, Powell SK, Plummer RS, Young KP, Ruggeri BA. PAX genes: roles in development, pathophysiology, and cancer. *Biochem Pharmacol* 2007; **73**: 1-14 [PMID: 16904651 DOI: 10.1016/j.bcp.2006.06.024]
6 **Daniel L**, Lechevallier E, Giorgi R, Sichez H, Zattara-Cannoni H, Figarella-Branger D, Coulange C. Pax-2 expression in adult renal tumors.

*Hum Pathol* 2001; **32**: 282-287 [PMID: 11274636 DOI: 10.1053/hupa.2001.22753]
7 **Heidarpour M**, Tavanafar Z. Diagnostic utility of PAX8 in differentiation of mullerian from non-mullerian tumors. *Adv Biomed Res* 2014; **3**: 96 [PMID: 24800185 DOI: 10.4103/2277-9175.129366]
8 **Laury AR**, Hornick JL, Perets R, Krane JF, Corson J, Drapkin R, Hirsch MS. PAX8 reliably distinguishes ovarian serous tumors from malignant mesothelioma. *Am J Surg Pathol* 2010; **34**: 627-635 [PMID: 20414098 DOI: 10.1097/PAS.0b013e3181da7687]
9 **Adegoke O**, Kulasingam S, Virnig B. Cervical cancer trends in the United States: a 35-year population-based analysis. *J Womens Health (Larchmt)* 2012; **21**: 1031-1037 [PMID: 22816437 DOI: 10.1089/jwh.2011.3385]
10 **Guo F**, Cofie LE, Berenson AB. Cervical Cancer Incidence in Young U.S. Females After Human Papillomavirus Vaccine Introduction. *Am J Prev Med* 2018; **55**: 197-204 [PMID: 29859731 DOI: 10.1016/j.amepre.2018.03.013]
11 **Bewley S**. HPV vaccination and cervical cancer screening. *Lancet* 2022; **399**: 1939 [PMID: 35598621 DOI: 10.1016/S0140-6736(22)00110-6]
12 **Cree IA**, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: female genital tract tumours. *Histopathology* 2020; **76**: 151-156 [PMID: 31846528 DOI: 10.1111/his.13977]
13 **Kojima A**, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M, Nishimura R. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol* 2007; **31**: 664-672 [PMID: 17460448 DOI: 10.1097/01.pas.0000213434.91868.b0]
14 **Kumar L**, Pokharel YH, Dawar R, Thulkar S. Cervical cancer metastatic to the breast: a case report and review of the literature. *Clin Oncol (R Coll Radiol)* 1999; **11**: 414-416 [PMID: 10663334 DOI: 10.1053/clon.1999.9095]
15 **Cholmondeley K**, Callan L, Sangle N, D'Souza D. Metastatic cervical adenocarcinoma to the breast: A case report and literature review. *Gynecol Oncol Rep* 2019; **28**: 33-36 [PMID: 30815528 DOI: 10.1016/j.gore.2019.01.011]
16 **Maulbecker CC**, Gruss P. The oncogenic potential of Pax genes. *EMBO J* 1993; **12**: 2361-2367 [PMID: 8099544 DOI: 10.1002/j.1460-2075.1993.tb05890.x]
17 **Corona RI**, Seo JH, Lin X, Hazelett DJ, Reddy J, Fonseca MAS, Abassi F, Lin YG, Mhawech-Fauceglia PY, Shah SP, Huntsman DG, Gusev A, Karlan BY, Berman BP, Freedman ML, Gayther SA, Lawrenson K. Non-coding somatic mutations converge on the PAX8 pathway in ovarian cancer. *Nat Commun* 2020; **11**: 2020 [PMID: 32332753 DOI: 10.1038/s41467-020-15951-0]
18 **Fu DJ**, De Micheli AJ, Bidarimath M, Ellenson LH, Cosgrove BD, Flesken-Nikitin A, Nikitin AY. Cells expressing PAX8 are the main source of homeostatic regeneration of adult mouse endometrial epithelium and give rise to serous endometrial carcinoma. *Dis Model Mech* 2020; **13** [PMID: 32998907 DOI: 10.1242/dmm.047035]
19 **Di Palma T**, Lucci V, de Cristofaro T, Filippone MG, Zannini M. A role for PAX8 in the tumorigenic phenotype of ovarian cancer cells. *BMC Cancer* 2014; **14**: 292 [PMID: 24766781 DOI: 10.1186/1471-2407-14-292]
20 **Ramachandran D**, Wang Y, Schürmann P, Hülse F, Mao Q, Jentschke M, Böhmer G, Strauß HG, Hirchenhain C, Schmidmayr M, Müller F, Runnebaum I, Hein A, Koch M, Ruebner M, Beckmann MW, Fasching PA, Luyten A, Dürst M, Hillemanns P, Dörk T. Association of genomic variants at PAX8 and PBX2 with cervical cancer risk. *Int J Cancer* 2021 [PMID: 33905146 DOI: 10.1002/ijc.33614]
21 **Wu Y**, Li H, Wang H, Zhang F, Cao H, Xu S. MSK2 promotes proliferation and tumor formation in squamous cervical cancer *via* PAX8/RB-E2F1/cyclin A2 axis. *J Cell Biochem* 2019; **120**: 11432-11440 [PMID: 30756420 DOI: 10.1002/jcb.28421]
22 **Li CG**, Nyman JE, Braithwaite AW, Eccles MR. PAX8 promotes tumor cell growth by transcriptionally regulating E2F1 and stabilizing RB protein. *Oncogene* 2011; **30**: 4824-4834 [PMID: 21602887 DOI: 10.1038/onc.2011.190]
23 **Fraizer GC**, Shimamura R, Zhang X, Saunders GF. PAX 8 regulates human WT1 transcription through a novel DNA binding site. *J Biol Chem* 1997; **272**: 30678-30687 [PMID: 9388203 DOI: 10.1074/jbc.272.49.30678]
24 **Macchia PE**, Lapi P, Krude H, Pirro MT, Missero C, Chiovato L, Souabni A, Baserga M, Tassi V, Pinchera A, Fenzi G, Grüters A, Busslinger M, Di Lauro R. PAX8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. *Nat Genet* 1998; **19**: 83-86 [PMID: 9590296 DOI: 10.1038/ng0598-83]
25 **Shukla A**, Thomas D, Roh MH. PAX8 and PAX2 expression in endocervical adenocarcinoma in situ and high-grade squamous dysplasia. *Int J Gynecol Pathol* 2013; **32**: 116-121 [PMID: 23202787 DOI: 10.1097/PGP.0b013e318257df46]
26 **Goyal A**, Yang B. Differential patterns of PAX8, p16, and ER immunostains in mesonephric lesions and adenocarcinomas of the cervix. *Int J Gynecol Pathol* 2014; **33**: 613-619 [PMID: 25272301 DOI: 10.1097/PGP.0000000000000102]
27 **Huang SL**, Liu ZQ, Zhang XN, Li MJ. Human papillomavirus, human cytomegalovirus and oncogene C-myc in cervical carcinoma and cervicitis. *Chin Med J (Engl)* 1993; **106**: 208-210 [PMID: 8391967]
28 **Stenzel A**, Semczuk A, Rózyńskal K, Jakowicki J, Wojcierowski J. "Low-risk" and "high-risk" HPV-infection and K-ras gene point mutations in human cervical cancer: a study of 31 cases. *Pathol Res Pract* 2001; **197**: 597-603 [PMID: 11569923]
29 **Yemelyanova A**, Gown AM, Wu LS, Holmes BJ, Ronnett BM, Vang R. PAX8 expression in uterine adenocarcinomas and mesonephric proliferations. *Int J Gynecol Pathol* 2014; **33**: 492-499 [PMID: 25083965 DOI: 10.1097/PGP.0b013e3182a54afa]
30 **Danialan R**, Assaad M, Burghardt J, Newcomb P, Cartun RW, Mandavilli S. The utility of PAX8 and IMP3 immunohistochemical stains in the differential diagnosis of benign, premalignant, and malignant endocervical glandular lesions. *Gynecol Oncol* 2013; **130**: 383-388 [PMID: 23618832 DOI: 10.1016/j.ygyno.2013.04.020]

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