Increased expression of plakophilin 3 is associated with poor prognosis in ovarian cancer

Hua Qian, MD\textsuperscript{a}, Donglan Yuan, MD\textsuperscript{a}, Jingjing Bao, MD\textsuperscript{b}, Fuxing Liu, MD\textsuperscript{b}, Wenyen Zhang, MD\textsuperscript{b}, Xumei Yang, BS\textsuperscript{c}, Gaohua Han, MD\textsuperscript{d}, Junxing Huang, MD\textsuperscript{d}, Haihui Sheng, PhD\textsuperscript{d}, Hong Yu, MD\textsuperscript{b,∗}

Abstract

Considering the essential role of plakophilin 3 (PKP3) in the maintenance cell-cell adhesion, dysregulation of PKP3 is involved in human diseases. This study aimed to explore the clinical significance of PKP3 in ovarian cancer. Immunohistochemistry was performed to examine the PKP3 expression in 157 cancer specimens from primary ovarian cancer patients. PKP3 was expressed in both the cytoplasm and nucleus. Eighty-one (51.6\%) out of 157 ovarian cancer tissues showed PKP3 expression, while absent expression was observed in normal ovarian tissues. High PKP3 expression was associated with lymph node metastasis (LNM, \(P=0.04\)) and advanced International Federation of Gynecology and Obstetrics (FIGO) stage (\(P=0.013\)). Patients with high PKP3 expression had shorter overall survival (OS) than those with low PKP3 expression (60.2 months vs 74.2 months, \(P=0.021\)). However, no association between PKP3 expression and progression-free survival (PFS) was observed (\(P=0.790\)). Cox regression analysis indicated that PKP3 expression was an independent predictive factor for OS with patient with ovarian cancer (adjusted HR = 1.601, 95\%CI: 1.014-2.528, \(P=0.043\)), especially those with FIGO stages III and IV disease (adjusted HR = 1.607, 95\%CI: 1.006-2.567, \(P=0.047\)). The gene expression profiling interactive analysis (GEPIA) databases also showed that PKP3 was upregulated in ovarian cancer (\(P<0.001\)) and patients with high PKP3 expression had shorter OS (\(P=0.004\)). In conclusion, our findings suggest that PKP3 is upregulated in ovarian cancer and is likely involved in the progression of ovarian cancer. PKP3 might therefore serve as a prognostic biomarker for patients with ovarian cancer.

Abbreviations: 95\% CI = 95\% confidence interval, CDH17 = cadherin 17, CDH3 = cadherin 3, CTNNB1 = catenin beta 1, DCHS2 = dachous cadherin-related 2, FAT4 = FAT atypical cadherin 4, FBXO7 = F-box protein 7, FFPE = formalin-fixed paraffin-embedded, FIGO = International Federation of Gynecology and Obstetrics, GEPIA = gene expression profiling interactive analysis, H&E = haematoxylin and eosin, HR = hazard ratio, IHC = immunohistochemistry, LNM = lymph node metastasis, OR = odds ratio, OS = Overall survival, PFS = progression-free survival, PKP3 = plakophilin 3, TMA = tissue microarray, ZEB1 = zinc finger E-box binding homeobox 1.

Keywords: cell adhesion, desmosome, ovarian cancer, plakophilin 3, prognosis

1. Introduction

With the progression in the early detection and treatment, the incidence and mortality of ovarian cancer is declining in China.\textsuperscript{[1,2]} Ovarian cancer is the 11th most common cancer and the 10th leading cause of death from cancer in women, with an estimated 51,000 (3.0\%) new cases diagnosed and 23,000 (2.7\%) deaths in 2014.\textsuperscript{[3]} Most patients with ovarian cancer are diagnosed at late stages due to vague associated symptoms, and thus the overall prognosis of ovarian cancer remains poor, with an overall 5-year survival rate of less than 50\%.\textsuperscript{[3]} Since ovarian cancer exhibits highly invasive and metastatic properties and existing therapeutic strategies have limited efficacy for advanced disease, it is critical to understand the underlying molecular mechanism of the progression of ovarian cancer.

Epithelial cells are joined to each other by tight junctions, adherens junctions, and desmosomes.\textsuperscript{[4]} Desmosomes are important cell-cell junctional protein complex that tethers intermediate filaments cytoskeleton to the plasma membrane–spanning desmosomal cadherins via the armadillo (i.e., plakoglobin and plakophilin) and plakin (i.e., desmplakin, perilplakin, and envoplakin) proteins. Disruption of desmosomal adhesion caused by mutations in desmosomal genes, and autoantibodies or bacterial toxins targeting desmosomal cadherins has been linked to human diseases such as skin diseases and cardiomyopathies.\textsuperscript{[5]} It is not surprising that desmosomes play an important role in cancer progression since cancer invasion and metastasis require breaking down the junctions that hold cells together in a tissue.\textsuperscript{[6]}

Substantial evidence supports a tumor-inhibitory function of desmosomes that loss of desmosome proteins and desmosomal adhesion is involved in cancer development and progression. However, this may not be the case in all circumstances because
some desmosome proteins exhibit oncogenic potential in some types of human cancer.\textsuperscript{[6]} Plakophilin 3 (PKP3) is a member of the p120\textsuperscript{cm}/plakophilin subfamily of armadillo proteins that mediate the cytoplasmic associations with the cadherins. Unlike PKP1 and PKP2, PKP3 is ubiquitously expressed in all the layers of the stratified epithelium except hepatocytes.\textsuperscript{[7,8]} In addition to desmosomal functions, PKP3 also plays an important role in the regulation of protein synthesis, growth control, and transcription.\textsuperscript{[8–10]} Dysregulation of PKP3 is observed in various types of cancer including colon, lung, and bladder cancers, which is associated with the cancer progression.\textsuperscript{[11–15]} Knockdown of PKP3 leads to a decrease in desmosome size and cell-cell adhesion, and enhanced cancer cell metastasis and growth.\textsuperscript{[16]} However, upregulation of PKP3 is associated with the progression of breast and lung cancers.\textsuperscript{[9,14]} PKP3 seems to play a different role in different types of cancer. To date, there is little knowledge about the role of PKP3 in ovarian cancer. Considering its critical role in the progression of aforementioned cancers, this study aimed to investigate PKP3 expression in ovarian cancer as well as its clinical significance.

2. Materials and methods

2.1. Clinical tissue sample collection

This study was approved by the Ethics Committee of Taizhou people’s Hospital. The methods and experimental protocols of the present study were carried out in accordance with the approved guidelines of Taizhou people’s Hospital. Written informed consent was obtained from all patients. We used 157 formalin-fixed paraffin-embedded (FFPE) ovarian cancer tissues from 157 patients who underwent radical surgery between 2007 and 2010 at Taizhou people’s Hospital. The histological cell-type was defined according to the criteria of the World Health Organization classification. All patients were pathologically confirmed with epithelial ovarian cancer. No patients had received any anticancer therapy such as neoadjuvant chemotherapy, radiation therapy and immunotherapy prior to surgery. Progression-free survival (PFS) was defined as the time from the surgery until relapse, progressive disease, or last follow-up. Overall survival (OS) was defined as the time from the surgery until death from any cause or the last follow-up.

2.2. Immunohistochemistry (IHC)

Core tissues with a 1.5 mm diameter were taken from individual paraffin-embedded block and then embedded in the prepared hole in the acceptor block as described previously.\textsuperscript{[17]} Subsequently, sections with 4\,\mu m thickness were cut from the array blocks to make a tissue microarray (TMA). TMA was stained with haematoxylin and eosin (H&E) and validated by two pathologists. TMA sections was deparaaffinized by sequential washings with xylene, 100\% ethanol, 95\% ethanol, 80\% ethanol, and PBS. After antigen retrieval, endogenous peroxidase activity was blocked with 3\% hydrogen peroxide. Nonspecific epitopes were blocked through incubating the sections with 10\% goat serum in PBS at room temperature for 1 hour. TMA section was incubated with a primary monoclonal rabbit anti-PKP3 antibody (dilution 1:100; Abcam, Cambridge, MA, USA) overnight at 4°C and then incubated with horseradish peroxidase-conjugated goat anti-rabbit secondary antibody at room temperature for 1 hour. Known positive ovarian cancer was used as a positive control, whereas negative control was obtained by replacing primary antibody with PBS. Immunostained section was evaluated by two independent pathologists, who were blinded to each other’s scores as well as the clinical and pathological data.

2.3. Statistical analyses

Statistical analyses were performed using IBM SPSS software version 25.0 (SPSS Inc., IL) and GraphPad Prism 7 (GraphPad Software, CA). Two-sided P values <.05 were considered to be statistically significant for all statistical procedure. Continuous data were compared with the Mann-Whitney test. Fisher exact test was used to evaluated the association between clinicopathologic variables and PKP3 protein expression. Survival curves were estimated with the Kaplan–Meier method and compared by log-rank test. Factors with a value of P <.05 in the univariate analysis were further analyzed using a multivariate Cox proportional hazard model.

3. Results

3.1. Clinicopathological characteristics of patients with ovarian cancer

The retrospective analysis included medical records of 157 patients with ovarian cancer who underwent radical surgery between 2007 and 2010. Clinicopathological characteristics of patients were described in Table 1. Briefly, the median age at the diagnosis was 52.0 years (range from 20.0–75.0 years). The histological type of 157 patients was epithelial ovarian cancer with 129 (82.2\%) patients with serous and 28 (17.8\%) with non-serous type. Forty-two (26.8\%) patients had lymph node metastasis (LNM) and 33 (21.0\%) had distant metastasis at the time of diagnosis. The majority of cases were poorly differentiated (72.5\%). The vast majority of patients (71.3\%) had FIGO stage IV.

| Table 1 | Clinical characteristics of patients with ovarian cancer. |
|---|---|
| **General characteristics** | All (n = 157) |
| Age at primary diagnosis (years) | 50.9 ± 11.6 |
| Follow-up period (month) | Median: 64.0 (4.0–110.0) |
| Diameter of the tumor (cm) | Median: 12.5 (1.9–25.5) |
| Status | |
| Survival | 72 (45.9) |
| Death | 85 (54.1) |
| Histological type | |
| Serous | 129 (82.2) |
| Others | 28 (17.8) |
| Histologic grade | |
| 1 | 15 (9.6) |
| 2 | 15 (9.6) |
| 3 | 127 (80.9) |
| Lymph node status | |
| Negative | 115 (73.2) |
| Positive | 42 (26.8) |
| Distant metastasis | |
| Negative | 124 (79.0) |
| Positive | 33 (21.0) |
| FIGO stage | |
| I | 9 (5.7) |
| II | 36 (22.9) |
| III | 79 (50.3) |
| IV | 33 (21.0) |

FIGO = International Federation of Gynecology and Obstetrics.
were classified as International Federation of Gynecology and Obstetrics (FIGO) stage III and IV. The median PFS and OS survival time were 41.0 months (95%CI: 30.9–51.1) and 75.0 months (95%CI: 51.5–98.5), respectively.

3.2. Upregulation of PKP3 in ovarian cancer

IHC was used to evaluate the expression levels of PKP3 in 157 ovarian cancer specimens. PKP3 protein expression showed both nuclear and/or cytoplasmic staining in ovarian cancer.

Figure 1. PKP3 was upregulated in ovarian cancer. A, negative staining of PKP3 in normal ovarian tissue. B, negative staining of PKP3 in ovarian cancer tissue. C, weak cytoplasmic staining of PKP3 in ovarian cancer tissue. D, strong cytoplasmic and weak nuclear staining of PKP3 in ovarian cancer tissue. E, the GEPIA database revealed that PKP3 expression was significantly upregulated in ovarian cancer tissues (n=426) compared with normal ovarian tissues (n=88). *P<.05. F, there was no significant difference in PKP3 between different pathologic stage of ovarian cancer based on the GEPIA database. GEPIA = gene expression profiling interactive analysis, PKP3 = plakophilin 3.
protein expression was negative in normal ovarian tissues, whereas ovarian cancer tissues displayed significantly increased expression of PKP3 (Fig. 1). Positive cytoplasmic staining of PKP3 was observed in 81 (51.6%) cases, among which 6 (7.4%) cases showed strong PKP3 expression. In addition, 14 cases with cytoplasmic staining of PKP3 also showed nuclear staining of PKP3. The expression levels of PKP3 in ovarian cancer tissues were higher than those in normal ovarian tissues \( (P < .001) \). We further evaluated PKP3 expression using the gene expression profiling interactive analysis (GEPIA) database.\[^{18}\] The results revealed that the expression levels of PKP3 in 426 ovarian cancer tissues were higher than those in 88 normal ovarian tissues (Fig. 1), which was consistent with the IHC results. There was no correlation between pathological stage and the PKP3 expression level \( (P > .05) \).

### 3.3. Association between PKP3 expression and clinicopathological features of ovarian cancer

To explore the role of PKP3 in the progression of ovarian cancer, we further analyzed the associations between PKP3 expression and clinicopathological features of ovarian cancer. As shown in Table 2, high PKP3 expression was associated with LNM \( (P = .004) \) and advanced FIGO stage \( (P = .013) \). No association between PKP3 expression and age, tumor size, pathologic type, histologic grade and distant metastasis was observed \( (P > .05) \).

### 3.4. Survival analyses

We also evaluated the effect of PKP3 on the survival of patients with ovarian cancer. The median OS time in patients with high PKP3 expression was 60.2 months, which was significantly longer than that in patients with low PKP3 expression (74.2 months, \( P = .009 \), Fig. 2). There was no significant association between PKP3 expression and PFS \( (P = .709) \). The prognostic role of PKP3 in ovarian cancer was then assessed using the GEPIA database. High PKP3 expression was significantly associated with shorter OS \( (P = .004) \) but not PFS \( (P = .69) \), which were in agreement with our results.

Furthermore, univariate analysis using Cox proportional hazard model showed that larger tumor size (hazard ratio \( [HR] = 3.459, 95\% CI: 2.124–5.929, P < .001 \)), LNM (HR = 5.541, 95\% CI: 3.560–8.625, \( P < .001 \)), distant metastasis (HR = 5.687, 95\% CI: 3.563–9.078, \( P < .001 \)), advanced FIGO stage (HR = 2.338, 95\% CI: 1.672–3.270, \( P < .001 \)), and high PKP3 expression (HR = 2.128, 95\% CI: 1.366–3.314, \( P < .001 \)) were associated with poor OS (Table 3). In the multivariate analysis, larger tumor size (adjusted HR = 2.797, 95\% CI: 1.624–4.815, \( P < .001 \)), LNM (adjusted HR = 2.237, 95\% CI: 1.175–4.257, \( P = .014 \)), advanced FIGO stage (adjusted HR = 1.987, 95\% CI: 1.409–2.802, \( P < .001 \)), and high PKP3 expression (adjusted HR = 1.601, 95\% CI: 1.014–2.528, \( P = .043 \)) were independent unfavorable prognostic factors for OS in patients with ovarian cancer. Further analysis revealed that this effect was existed in patients with FIGO stages III and IV disease (adjusted HR = 1.607, 95\% CI: 1.006–2.567, \( P = .047 \)) (Table 4).

### 3.5. Prediction of interaction networks of PKP3

To identify the genes that could interact with PKP3, we conducted an interaction network prediction using STRING v10.5,\[^{19}\] which were further validated using GEPIA to increase the credibility of the conclusion.\[^{18}\] The genes with the top 20 scores were listed in Table S1, http://links.lww.com/MD/C848. The protein-protein interaction (PPI) network of the top 20 genes was shown in Figure 3. Subsequently, these PPIs were further examined using GEPIA based on the result in the STRING protein query from public databases. The results revealed that PPIs predicted using STRING and GEPIA were consistent except for catenin beta 1 (CTNNB1), F-box protein 7 (FBXO7),

### Table 2

**Association of PKP3 expression with clinicopathologic parameters.**

| Variables                        | PKP3 expression |
|----------------------------------|-----------------|
|                                  | High            | Low             | \( P \) value |
| Age (years)                      |                 |                 |               |
| < 55                             | 50 (53.8)       | 43 (46.2)       | .515          |
| \( \geq 55 \)                     | 30 (47.6)       | 33 (52.4)       |               |
| Histological type                |                 |                 |               |
| Serous                           | 71 (55.0)       | 58 (45.0)       | .004          |
| Non-serous                       | 10 (35.7)       | 18 (64.3)       |               |
| Tumor size (cm)                  |                 |                 |               |
| < 10                             | 29 (46.0)       | 34 (46.0)       | .260          |
| \( \geq 10 \)                     | 52 (55.3)       | 42 (44.7)       |               |
| LNM                              |                 |                 |               |
| non-LNM                          | 51 (44.3)       | 64 (55.7)       | .004          |
| LNM                              | 30 (71.4)       | 12 (28.6)       |               |
| Distant metastasis               |                 |                 |               |
| Negative                         | 61 (49.2)       | 63 (50.8)       | .327          |
| Positive                         | 20 (60.6)       | 13 (39.4)       |               |
| FIGO stage                       |                 |                 |               |
| I + II                           | 16 (35.6)       | 29 (64.4)       | .013          |
| III + IV                         | 65 (69.0)       | 47 (42.0)       |               |

\( \text{FIGO} = \text{International Federation of Gynecology and Obstetrics}, \text{LNM} = \text{lymph node metastasis}, \text{PKP3} = \text{plakophilin 3}. \)
cadherin 3 (CDH3), cadherin 17 (CDH17), and dachsous cadherin-related 2 (DCHS2). Thirteen genes were positively correlated with PKP3, whereas FAT atypical cadherin 4 (FAT4) and Zinc finger E-box binding homeobox 1 (ZEB1) were negative correlated with PKP3.

4. Discussion
Recurrence and metastasis are critical causes of cancer-related death. It is important to understand the underlying molecular and cellular processes involved in the regulation of ovarian cancer metastasis. Cell-cell adhesion and interactions mediated by PKP3...
adhesive junction components are essential for the maintenance of the structural integrity of tissues. Disruption of adhesive junctional complexes plays a causal role in the promotion of invasion and metastasis. Loss of cell adhesion contacts confer a highly motile and invasive phenotype on cancer cells and thus enables them to dissociate from the primary mass. As a result, cancer cells eventually invade and spread to adjacent or distant organs.

PKPs that are characteristic plaque proteins of desmosomes assist in assembling and stabilizing cadherins at the plasma membrane and bind them to the intermediate filament cytoskeleton.[20–23] Dual nuclear and cytoplasmic localization of PKPs suggests that they have diverse nondesmosomal functions such as regulation of transcription and translation, growth control, and the trafficking of desmosomal cadherins,[18–10,24] but not fully understood. Loss or reduction of PKP1 and PKP3 is frequently observed in various types of human cancer including colon, prostate, and gastric cancers, associated with their malignant behavior,[11,16,24–26] whereas PKP2 seems likely to have a potentially oncogenic role in human cancer.[27,28] In addition, PKP3 also exhibits oncogenic potential in breast and lung cancers.[9,14] Therefore, PKP3 might have tumor-suppressor and oncogenic potentials in different types of cancer depending on the cellular context. In the present study, PKP3 was expressed in 51.6% of ovarian cancer tissues but was not expressed in normal ovarian tissues. High PKP3 expression was associated with LNM and advanced FIGO stage. Survival analysis revealed that high PKP3 expression was associated with a higher probability of mortality. This result indicates the prognostic potential of PKP3 in ovarian cancer. To further confirm these results, we assessed PKP3 expression in the GEPIA database. We found that the expression levels of PKP3 in ovarian cancer tissues were dramatically higher than those in normal ovarian tissues, and high PKP3 expression was associated with poor prognosis, which was consistent with our findings. These results imply that PKP3 might serve as a novel potential biomarker for ovarian cancer and is involved in the progression of ovarian cancer. This study, to the best of our knowledge, was the first to evaluate the clinical significance of PKP3 in ovarian cancer. Combined with IHC assay and GEPIA data, we confirmed that PKP3 was upregulated in ovarian cancer tissues, and high PKP3 expression may play an important role in ovarian cancer.

To identify the genes that might have an interaction with PKP3, we conducted PPI analysis using the STRING database and further validated using the GEPIA database. The top 20 genes interacting with PKP3 were enriched in cell-cell junction pathways. Only 15 interaction nodes further reach statistical significance in the GEPIA database. Among these genes, FAT4 and ZEB1 exhibited the negative correlations with PKP3. ZEB1 can bind directly to the PKP3 promoter and represses its transcription.[13] Therefore, downregulation of ZEB1 in ovarian cancer leads to the upregulation of PKP3.[13,29] In addition, 14 (8.9%) cases showed nuclear staining of PKP3, which indicated that nuclear PKP3 might participate in transcription regulation through interacting with transcription factor. Further studies are necessary in order to elucidate the role of nuclear PKP3 in ovarian cancer.

In conclusion, our findings provided the first evidence that PKP3 is upregulated in ovarian cancer and may serve as a novel prognostic biomarker for ovarian cancer. However, the underlying molecular mechanism by which PKP3 contributed to malignant behavior of ovarian cancer requires further research.

### Author contributions
Conception and design: HQ and HY; provision of study materials or patients: HQ, DY, HS, and HY; collection and assembly of data: DY, JB, FL, WZ, and XY; data analysis and interpretation: GH, JH, and HS; manuscript writing: HQ, DY, and HY; final approval of manuscript: all authors.

#### Table 3
Univariate and multivariate Cox regression analysis of overall survival in 157 ovarian cancer cases.

| Variables                           | Univariate analysis | Multivariate analysis |
|-------------------------------------|---------------------|-----------------------|
|                                     | HR (95% CI)         | P value               | HR (95% CI)         | P value               |
| Age (years), < 55 vs ≥ 55           | 1.459 (0.950–2.241) | .085                  | 2.797 (1.624–4.815) | < .001                |
| Histological type, serous vs non-serous | 0.532 (0.275–1.030) | .061                  |                      |                       |
| Histologic grade, 2 + 3 vs 1        | 1.253 (0.827–1.899) | .287                  | 2.237 (1.175–4.257) | .014                  |
| Tumor size (cm), ≥ 10 vs < 10       | 3.549 (2.124–5.929) | < .001                | 1.494 (0.755–2.956) | .248                  |
| LNM, positive vs negative           | 5.541 (3.560–8.625) | < .001                | 1.987 (1.409–2.602) | < .001                |
| Distant metastasis, positive vs negative | 5.687 (3.503–9.078) | < .001                | 1.601 (1.014–2.528) | .043                  |
| FIGO stage, III + IV vs I + II      | 2.338 (1.672–3.270) | < .001                |                      |                       |
| PKP3 expression, positive vs negative | 2.128 (1.366–3.314) | < .001                |                      |                       |

**FIGO** = International Federation of Gynecology and Obstetrics, **LNM** = lymph node metastasis, **PKP3** = plakophilin 3.

#### Table 4
PKP3 expression and OS of patients with ovarian cancer by clinicopathologic parameters.

| Variables                           | HR (95% CI) | P value |
|-------------------------------------|-------------|---------|
| Age (years)                         |             |         |
| < 55                                | 1.479 (0.800–2.735) | .212    |
| ≥ 55                                | 1.677 (0.810–3.471) | .164    |
| Histological type                   |             |         |
| Serous                              | 1.569 (0.959–2.568) | .073    |
| Non-serous                          | 1.322 (0.311–6.622) | .706    |
| Histologic grade                    |             |         |
| 1                                   | 1.530 (0.307–7.628) | .604    |
| 2 + 3                               | 1.555 (0.964–2.508) | .071    |
| Tumor size (cm)                     |             |         |
| < 10                                | 1.736 (0.719–4.196) | .220    |
| ≥ 10                                | 1.471 (0.868–2.493) | .151    |
| LNM                                 |             |         |
| Non-LNM                             | 1.560 (0.854–2.850) | .148    |
| LNM                                 | 1.706 (0.806–3.610) | .163    |
| FIGO stage                          |             |         |
| I + II                              | 1.402 (0.210–10.611) | .690    |
| III + IV                            | 1.429 (0.919–2.224) | .113    |

**FIGO** = International Federation of Gynecology and Obstetrics, **LNM** = lymph node metastasis, **PKP3** = plakophilin 3.

*Adjusted for age, tumor size, grade, pathologic type, LNM, and FIGO stage, as appropriate.*
**Conceptualization:** Hua Qian, Hong Yu.
**Data curation:** Donglan Yuan, Jingjing Bao, Fuxing Liu, Wenyan Zhang, Xumei Yang.
**Formal analysis:** Gaohua Han, Junxing Huang, Haihui Sheng.
**Funding acquisition:** Hua Qian, Hong Yu.
**Methodology:** Hua Qian, Donglan Yuan, Wenyan Zhang, Xumei Yang.
**Resources:** Haihui Sheng.
**Writing – original draft:** Hua Qian, Donglan Yuan, Hong Yu.
**Writing – review & editing:** Hua Qian, Hong Yu.

---

**Figure 3.** PPI network analysis of PKP3 with other genes. Top 20 candidate genes might have an interaction with PKP3. PKP3 = plakophilin 3.

---

**References**

[1] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[2] Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. Chin J Cancer Res 2018;30:1–2.
[3] Zhang L, Cao X, Zhang L, et al. UCA1 overexpression predicts clinical outcome of patients with ovarian cancer receiving adjuvant chemotherapy. Cancer Chemother Pharmacol 2016;77:629–34.
[4] Capaldo CT, Farkas AE, Nusrat A. Epithelial adhesive junctions. F1000Prime Rep 2014;6:1.
[5] Najor NA. Desmosomes in human disease. Annu Rev Pathol 2018;13:51–70.
[6] Zhou G, Yang L, Gray A, et al. The role of desmosomes in carcinogenesis. Onco Targets Ther 2017;10:4059–63.
[7] Schmidt A, Langbein L, Pratzel S, et al. Plakophilin 3–a novel cell-type-specific desmosomal plaque protein. Differentiation 1999;64:291–306.
[8] Bass-Zubek AF, Godiel LM, Delmar M, et al. Plakophi: multifunctional scaffolds for adhesion and signaling. Curr Opin Cell Biol 2009;21:708–16.
[9] Hatzfeld M, Wolf A, Keil R. Plakophilins in desmosomal adhesion and signaling. Cell Commun Adhes 2014;21:25–42.
[10] Munoz WA, Lee M, Miller RK, et al. Plakophilin-3 catenin associates with the ETV1/ER81 transcription factor to positively modulate gene activity. PLoS One 2014;9:e86784.
[11] Basu S, Chaudhary N, Shah S, et al. Plakophilin3 loss leads to an increase in lipocalin2 expression, which is required for tumor formation. Exp Cell Res 2018;369:251–65.
[12] Takahashi H, Nakatsuji H, Takahashi M, et al. Up-regulation of plakophilin-2 and Down-regulation of plakophilin-3 are correlated with invasiveness in bladder cancer. Urology 2012;79:e1–8. 240.
[13] Aigner K, Descovich L, Mikula M, et al. The transcription factor ZEB1 (deltaEF1) represses Plakophilin 3 during human cancer progression. FEBS Lett 2007;581:1617–24.
[14] Furukawa C, Daigo Y, Ishikawa N, et al. Protein binding and functional characterization of plakophilin 2. Evidence for its diverse roles in desmosomes and beta-catenin signaling. J Biol Chem 2002;277:10512–22.
[15] Li Y, Ju K, Wang W, et al. Dinitrosopiperazine-decreased PKP3 through upregulating miR-149 participates in nasopharyngeal carcinoma metastasis. Mol Carcinog 2018;57:1763–79.
[16] Breuninger S, Reidenbach S, Sauer CG, et al. Desmosomal plakophilins in the prostate and prostatic adenocarcinomas: implications for diagnosis and tumor progression. Am J Pathol 2010;176:2309–19.
[17] Kazlauskas A. Plakophilin-2 promotes activation of epidermal growth factor receptor. Mol Cell Biol 2014;34:3778–9.
[18] Benduraite A, Knouf EC, Garg KS, et al. Regulation of miR-200 family microRNAs and ZEB transcription factors in ovarian cancer: evidence supporting a mesothelial-to-epithelial transition. Gynecol Oncol 2010;116:117–25.