Reduction of Tat-interacting Protein 30 Expression Could be a Prognostic Marker in Bladder Urothelial Cancer

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Abstract

Background: Tat-interacting protein 30 (TIP30) has been reported to be a tumor suppressor, with reduced or absent expression in various tumors. However, its role in bladder urothelial cancer (BUC) has not been investigated. Therefore, herein, we investigated the expression of TIP30 protein in BUC and normal bladder mucosa and the clinical significance of TIP30 expression in the prognosis of BUC.

Methods: We reviewed data from 79 cases of BUC and 15 adjacent tissue samples from 79 patients treated at our institution between 2004 and 2007. TIP30 expression was examined by immunohistochemistry. The relationship between TIP30 expression and tumor stage, histological grade, and survival was analyzed. Differences between groups were evaluated using the t-test or matched-pairs test, and differences in the survival rates were analyzed with the log-rank test.

Results: TIP30 protein expression was significantly reduced in BUC tissue (t = -6.91, P < 0.05) compared with normal tissue samples, and in invasive bladder cancer (t = 10.89, P < 0.05) compared with superficial bladder cancer. TIP30 protein expression differed significantly among different differentiated groups classified either according to the World Health Organization (2004, F = 17.48, P < 0.01) or World Health Organization (1973, F = 10.68, P < 0.01). TIP30 protein expression was significantly reduced in high-grade papillary urothelial carcinoma compared with papillary urothelial neoplasm of low malignant potential (P < 0.05) and low-grade papillary urothelial carcinoma (P < 0.05). Meanwhile, TIP30 protein expression was significantly reduced in Grade III BUC, compared with Grade I (P < 0.05) and Grade II (P < 0.05). Patients with low TIP30 expression showed a higher incidence of disease progression than those with high TIP30 expression (t = 2.63, P < 0.05). Kaplan-Meier survival analysis showed a strong positive relationship between TIP30 expression and overall survival (OS) (χ² = 17.29, P < 0.05).

Conclusions: TIP30 expression was associated with clinical tumor stage in BUC, suggesting that it might play an important role in disease progression. Furthermore, TIP30 might predict postoperative OS. Thus, its evaluation might be useful for predicting prognosis.

Key words: Bladder Urothelial Cancer; Overall Survival Time; Tat-interacting Protein 30

Introduction

Bladder urothelial cancer (BUC) is among the most common malignancies worldwide. A total of 74% cases of bladder cancers are superficial at the time of diagnosis.[1] Approximately 50% of patients with superficial bladder cancers experience a recurrence within 6–12 months, and approximately 5–30% show progression to muscle-invasive cancer that has a 60–70% 5-year mortality.[2] Valuable predictors of recurrence are extremely limited for patients with bladder cancer, with the exception of tumor stage and grade, as well as the presence of carcinoma in situ. Therefore, the discovery of new and more effective biomarkers for bladder cancer is critical, not only for accurate evaluation of tumor recurrence and progression but also as a target for anticancer therapy.

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The human gene Tat-interacting protein 30 (TIP30), also known as CC3 or HITATIP2, was first identified as a suppressor of variant small-cell lung carcinoma (vSCLC). TIP30 expression is downregulated in various tumors with poor prognosis such as vSCLC, glioblastoma, breast carcinoma, gastric carcinoma, hepatocellular cancer, laryngeal carcinoma, esophageal carcinoma, colorectal cancer, lung cancer, and pancreatic cancer. TIP30 shows a positive effect in inhibiting cancer development and progression; however, its role in BUC has not previously been investigated.

In the present study, we performed immunohistochemistry (IHC) on tissue microarrays (TMAs) that contained BUC and normal bladder mucosa to investigate TIP30 expression, and analyzed the relationship between TIP30 and clinicopathological features. We aimed to investigate the expression and clinical significance of TIP30 in BUC. In addition, the correlation between TIP30 expression and prognosis was also analyzed. TIP30 might be a prognostic marker for BUC and a valuable target for the treatment on patients with BUC.

**Methods**

**Ethical approval**

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the institute (No: 2016010). Written informed consent was obtained from all patients or their guardians for children, before study enrollment.

**Patients and follow-up**

Tissues from patients with BUC were retrospectively identified from the Department of Pathology of the First Affiliated Hospital of Wenzhou Medical University between 2004 and 2007. None of these patients received preoperative chemoradiotherapy within 3 months of surgery. All patients who were treated with transurethral resection (TUR) of the bladder tumor or with partial cystectomy and who were histopathologically confirmed to have BUC were monitored through cystoscopy and urine cytology every 3 months during the first 2 years. From the 3rd year, patients without recurring malignancy were evaluated once per year. All cases were classified both according to the World Health Organization (2004) and World Health Organization (1973) for grade. Normal bladder mucosal specimens were obtained via TUR or partial cystectomy and used as controls. Recurrence was defined as the diagnosis of a new pTa or pT1 tumor, while progression was defined in terms of the development of muscle invasive lesions (pT2 or higher) or metastasis, or both.

**Tissue specimens and tissue microarray building**

A total of 79 samples of BUC, along with 15 specimens of the normal bladder mucosa, were included in this study. TMAs were prepared as described previously by Kononen et al. A fresh hematoxylin and eosin (H and E)-stained section was prepared from each donor tissue block and used as a guide to define the morphologically representative regions of the tumor or normal mucosa for subsequent sampling. The chosen regions of each donor block were punched with a 0.6-mm diameter tissue cylinder and transferred to the donor paraffin-embedded block (recipient block). A 4-mm section was stained with H and E to assess the presence of the target tissue through light microscopy.

**Immunohistochemistry**

We immunohistochemically processed 4-μm sections from the formalin-fixed, paraffin-embedded TMA. We deparaffinized the TMA sections in xylene, and re-hydrated them in descending dilutions of ethanol. Epitope retrieval was induced through heat treatment at 100°C for 15 min. We used the LabVision™ Autostainer 360 (Thermo Fisher Scientific, Inc., Fremont, CA, USA) to perform immunostaining. We then incubated the sections with 0.3% hydrogen peroxidase to block endogenous peroxidase activity (30 min at room temperature).

The slides were incubated overnight in the Autostainer with an antibody against TIP30 according to the manufacturer’s recommendation (1:200; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Nuclei were counterstained with hematoxylin. The positive control sample was normal bladder mucosa, and the negative control was the same normal tissue without the antibody.

**Evaluation of immunostaining**

Image-Pro Plus 6.0 (IPP6.0, MediaCybernetics, Inc., Bethesda, MD, USA) was used to analyze the immunoreactivity levels of TIP30. The measurement parameter was the integrated optical density (A). All images were verified by two pathologists who were blinded to the results of the previous assessments. In cases of disagreement, a consensus was reached by discussion.

**Statistical analysis**

Data analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The differences between groups were evaluated using the t-test or matched-pairs test. All statistical tests were two-tailed. The curves for disease-free survival (DFS) and overall survival (OS) were drawn using the Kaplan-Meier method, and differences in the survival rates were analyzed using the log-rank test. Prognostic factors were evaluated through univariate and multivariate analyses (Cox proportional hazards regression model). Continuous variables with normal distribution were presented as means ± standard deviation (SD), while skewed distributed variables were expressed as median (range). A value of $P < 0.05$ was considered statistically significant. DFS was measured from the surgical resection day until either recurrence or death without recurrence, and it was censored only for patients who were alive without evidence of recurrence at the last follow-up. OS was counted from the day of surgical resection until death from any cause and was censored only for patients known to be alive at last follow-up.


**RESULTS**

**Patient characteristics**

The clinicopathologic characteristics of the 79 patients are summarized in Table 1. Patients with tumors consisted of nine women and 70 men, and 15 of these also had normal mucosa (seven women and eight men). The mean age at presentation was 68.8 ± 11.1 years (range, 37–91 years). Tumor specimens were obtained through TUR (n = 75; 94.9%) or partial cystectomy (n = 4; 5.1%), and 15 samples of normal mucosal tissue were obtained using the same method during surgeries. The tumor group included 39 primary tumors and 40 recurrences. The series contained 9 pTa, 51 pT1, and 19 pT2–3 tumors, among which eight, 41, and 30 were classified as papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma (LG), and high-grade papillary urothelial carcinoma (HG), respectively, and 25, 28, and 26 were classified as Grade I, II, and III, respectively. The median follow-up period for all patients was 60.7 ± 29.2 months (range, 6–159 months).

**Tat-interacting protein 30 expression in tissue microarray sections**

IHC staining for TIP30 protein was identified in the cytoplasm of both normal mucosa and BUC specimens [Figure 1]. Representative images of TIP30 IHC staining are shown in Figure 1. TIP30 expression in patients with BUC was significantly decreased compared with that in normal mucosa (0.549 ± 0.065 vs. 0.663 ± 0.066, t = −6.91, P < 0.01). These data suggest that decreased TIP30 expression might be involved in the carcinogenesis of BUC. TIP30 protein expression differed significantly among different differentiated groups classified according to the World Health Organization (2004) (F = 17.48, P < 0.01) or World Health Organization (1973) (F = 10.68, P < 0.01). TIP30 expression did not differ significantly between PUNLMP and LG BUC (P = 0.97), however, it was significantly reduced in HG BUC compared with PUNLMP (P < 0.05) and LG BUC (P < 0.05). Meanwhile, TIP30 expression did not differ significantly between Grade I and Grade II BUC (P = 0.45), however, it was significantly reduced in Grade III BUC, compared with Grade I (P < 0.05) and Grade II (P < 0.05). TIP30 expression in the muscle-invasive stage was significantly lower than that in the nonmuscle-invasive stage (t = 10.89, P < 0.01). Patients with low TIP30 expression showed a higher incidence of tumor progression compared with those with high TIP30 expression (t = 2.63, P < 0.05). This result indicates that reduced TIP30 expression might be correlated with the progression and prognosis of BUC. TIP30 expression in patients treated with TUR was significantly higher than that in those treated with partial cystectomy (t = 4.02, P < 0.01). Furthermore, no significant differences in TIP30 expression were observed with regard to age, sex, tumor number, or tumor size of patients with BUC (P > 0.05).

**Correlation between Tat-interacting protein 30 expression and bladder urothelial cancer prognosis**

In this study, the median A of patients with BUC was 0.372. All patients were assigned to either a high TIP30 expression group (A ≥0.372) or a low TIP30 expression group (A <0.372).

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**Table 1: Correlations between TIP30 expression and clinicopathological characteristics of patients with BUC**

| Characteristics | n    | Mean density | t/F  | P     |
|-----------------|------|--------------|------|-------|
| **Sex**         |      |              |      |       |
| Male            | 70   | 0.3857 ± 0.1549 | 0.65* | 0.52  |
| Female          | 9    | 0.3496 ± 0.1770 |      |       |
| **Age**         |      |              |      |       |
| ≤65 years       | 28   | 0.3692 ± 0.1329 | −0.55* | 0.58  |
| >65 years       | 51   | 0.3884 ± 0.1693 |      |       |
| **Tumor grade (WHO2004)** |      |              |      |       |
| PUNLMP           | 8    | 0.4911 ± 0.1300 | 17.48* | <0.01 |
| LG               | 41   | 0.4408 ± 0.1237 |      |       |
| HG               | 30   | 0.2715 ± 0.1416 |      |       |
| **Tumor grade (WHO1973)** |      |              |      |       |
| Grade I          | 25   | 0.4598 ± 0.1170 | 10.68* | <0.01 |
| Grade II         | 28   | 0.4037 ± 0.1522 |      |       |
| Grade III        | 26   | 0.2828 ± 0.1472 |      |       |
| **Tumor size**   |      |              |      |       |
| ≥3 cm            | 39   | 0.3616 ± 0.1751 | 1.12* | 0.27  |
| <3 cm            | 40   | 0.4011 ± 0.1359 |      |       |
| **Treatment method** |       |              |      |       |
| TUR              | 75   | 0.3966 ± 0.1455 | 4.02* | <0.01 |
| Partial cystectomy | 4   | 0.1010 ± 0.0782 |      |       |
| **Tumor multiplicity** |       |              |      |       |
| Single           | 32   | 0.3783 ± 0.1692 | −0.15* | 0.88  |
| Multiple         | 47   | 0.3839 ± 0.1494 |      |       |
| **Clinical tumor stage** |      |              |      |       |
| Superficial      | 60   | 0.4450 ± 0.1156 | 10.89* | <0.01 |
| Muscle invasive  | 19   | 0.1814 ± 0.0831 |      |       |
| Recurrence       |      |              |      |       |
| No               | 39   | 0.4096 ± 0.1801 | 1.58* | 0.12  |
| Yes              | 40   | 0.3543 ± 0.1263 |      |       |
| Progression      |      |              |      |       |
| No               | 51   | 0.4107 ± 0.1733 | 2.63* | 0.01  |
| Yes              | 28   | 0.3286 ± 0.1040 |      |       |

*P* value; †F value. TIP30: Tat-interacting protein 30; BUC: Bladder urothelial cancer; PUNLMP: Papillary urothelial neoplasm of low malignant potential; LG: Low-grade papillary urothelial carcinoma; HG: High-grade papillary urothelial carcinoma; TUR: Transurethral resection.

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**Figure 1:** TIP30 expression in BUC and normal urothelium on IHC.

(a) Weak TIP30 staining in the cytoplasm of high-grade BUC (×200).
(b) Strong TIP30 staining in the cytoplasm of BUC with normal bladder mucosa (×200). TIP30: Tat-interacting protein 30; BUC: Bladder urothelial cancer; IHC: Immunohistochemistry.
Figures 2 and 3 show the Kaplan-Meier survival curves for patients with BUC tumors with high or low TIP30 expression. The OS of patients with low TIP30 expression was significantly lower than that of patients with high TIP30 protein expression ($\chi^2 = 17.29, P < 0.001$; Figure 2). However, the DFS of the two groups did not significantly differ ($\chi^2 = 0.15, P = 0.70$; Figure 3).

The results of univariate and multivariate analyses for the DFS of patients with BUC are shown in Table 2. Univariate analysis showed that TIP30 protein expression ($\chi^2 = 13.32, P < 0.01$), tumor grade ($\chi^2 = 15.48, P < 0.01$), and tumor stage ($\chi^2 = 8.60, P < 0.01$) were significant prognostic factors of OS. However, age, sex, size, and number of tumors had no prognostic significance ($P = 0.21, 0.22, 0.97, and 0.12$, respectively). Meanwhile, multivariate analyses showed that TIP30 protein expression ($\chi^2 = 5.55, P = 0.02$) and tumor grade ($\chi^2 = 15.18, P < 0.01$) were significant prognostic factors of OS.

**Discussion**

As a putative tumor suppressor gene, TIP30 is decreased in several cancer cell types and is involved in the regulation of tumor cell growth and metastasis.[9] As a transcription cofactor, TIP30 may suppress the expression of genes that are involved in proliferation, apoptosis, angiogenesis, and metastasis,[12-23] suggesting that TIP30 may act as a cancer suppressor. For example, overexpression of TIP30 has been shown to suppress tumor invasion through the extracellular matrix.[9] The restoration of TIP30 expression resulted in reduced expression of cyclin D1, Bcl-2, and Bcl-xl, but also led to overexpression of p27, Bax, p53, and caspase 3 and 9; resulted in cell cycle G0/G1 arrest; induced apoptosis in human gastric cancer-derived cells; and led to significantly attenuated tumor growth and abrogation of metastasis in mouse models.[10] Moreover, previous studies showed similar results, demonstrating that TIP30 overexpression in various cell lines resulted in increased expression of several proapoptotic genes and angiogenic inhibitors and reduced expression of angiogenic stimulators.[5,6,24]

Downregulation of TIP30 has been found to lead to expression of osteopontin, matrix metalloproteinase-2, and vascular endothelial growth factor, suggesting that downregulation of this protein promotes metastatic progression of lung cancer.[18] Chen and Shivelman[25] found that inhibition of TIP30 expression allowed tumor cells to evade apoptosis through glucose deprivation, and studies on animal models showed that TIP30–/– mice spontaneously developed tumors faster than wild-type mice.[26-27] Meanwhile, TIP30 knockdown led to prolonged epidermal growth factor receptor (EGFR) signaling in early endosomes, along with delayed EGFR degradation and increased EGFR nuclear location, leading to increased expression of pAKT and pERK1/2 in human lung adenocarcinoma cells.[27] TIP30 deletion enhanced proliferation of primary mammary epithelial cells and resulted in rapid immortalization of mammary epithelial cells in vitro relative to wild-type cells.[28]

The role of TIP30 in tumorigenesis is also evidenced by the reduced expression of TIP30 in human colorectal cancer.[17] The decreased TIP30 expression is associated with poor prognosis in patients with hepatocellular carcinoma.[12] Human hepatocellular carcinoma with methylated TIP30 has shown a tendency toward significantly high recurrence and mortality rates and low DFS.[25] TIP30 can also induce apoptosis and mitochondrial dysfunction, probably through stabilization of p53 mRNA, and this mechanism is blocked by inhibition of p53 expression.[6]

Comparison of the TIP30 cDNA sequences in the National Center for Biotechnology Information databases revealed the presence of TIP30 missense mutation in approximately 24% of various types of cancer cells.[26]

Therefore, TIP30 might play important roles in both the suppression of tumorigenesis and tumor invasion. However,
In summary, loss of TIP30 expression might be associated with BUC tumorigenesis and is an independent predictor for OS in patients with BUC. We believe that evaluation of TIP30 might assist in the development of new criteria for determining the prognosis of patients with BUC. Moreover, TIP30 might be a new and valuable target for the development of therapeutic strategies for patients with BUC.

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**Conflicts of interest**
There are no conflicts of interest.

**REFERENCES**
1. Ro JY, Staerkel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. Urol Clin North Am 1992;19:435-53. doi: 10.3410/f.71802059.793478732.
2. Hassen W, Droller MJ. Current concepts in assessment and treatment of bladder cancer. Curr Opin Urol 2000;10:291-9. doi: 10.1097/00042307-200007000-00002.
3. Shivelman E. A link between metastasis and resistance to apoptosis of variant small cell lung carcinoma. Oncogene 1997;14:2167-73. doi: 10.1038/sj.occ.1201059.
4. Dong X, Deng Q, Nie X, Zhang M, Jia W, Chen C, et al. Downregulation of HTATIP2 expression is associated with promoter methylation and poor prognosis in glioma. Exp Mol Pathol 2015;98:192-9. doi: 10.1016/j.yexmp.2015.01.013.
5. Hu Y, Chen F, Liu F, Liu X, Huang N, Cai X, et al. Overexpression of TIP30 inhibits the growth and invasion of glioma cells. Mol Med Rep 2016;13:605-12. doi: 10.3892/mmr.2015.4619.
6. Zhao J, Chen J, Lu B, Dong L, Wang H, Bi C, et al. TIP30 induces...
apoptosis under oxidative stress through stabilization of p53 messenger RNA in human hepatocellular carcinoma. Cancer Res 2008;68:4133-41. doi: 10.1158/0008-5472.CAN-08-0432.
7. Whitman S, Wang X, Shahab Y, Shitivelman E. Alternatively spliced products CC3 and TC3 have opposing effects on apoptosis. Mol Cell Biol 2000;20:583-93. doi: 10.1128/MCB.20.2.583-593.2000.
8. Huang QD, Hu XQ, Wang X, Zheng SR, You J, et al. Clinical significance of CC3/TIP30 expression in breast carcinoma and its correlation with HER-2/neu (in Chinese). Chin J Surg 2012;50:57-61. doi: 10.3760/cma.j.issn.0529-5815.2012.01.016.
9. Zhao J, Ni H, Ma Y, Dong L, Dai J, Zhao F, et al. TIP30/CC3 expression in breast carcinoma: Relation to metastasis, clinicopathologic parameters, and P53 expression. Hum Pathol 2007;38:293-8. doi: 10.1016/j.humpath.2006.08.005.
10. Li X, Zhang Y, Cao S, Chen X, Lu Y, Jin H, et al. Reduction of TIP30 correlates with poor prognosis of gastric cancer patients and its restoration drastically inhibits tumor growth and metastasis. Int J Cancer 2009;124:713-21. doi: 10.1002/ijc.23967.
11. Zhu M, Yin F, Fan X, Jing W, Chen R, Liu L, et al. Decreased TIP30 promotes Snail-mediated epithelial-mesenchymal transition and tumor-initiating properties in hepatocellular carcinoma. Oncogene 2015;34:1420-31. doi: 10.1038/onc.2014.73.
12. Fan SS, Liao CS, Cao YD, Xiao PL, Deng T, Luo RC, et al. A low serum Tat-interacting protein 30 level is a diagnostic and prognostic biomarker for hepatocellular carcinoma. Oncol Lett 2017;13:4208-14. doi: 10.3892/ol.2017.6024.
13. Zhao J, Zhang X, Shi M, Xu H, Jin J, Ni H, et al. TIP30 inhibits growth of HCC cell lines and inhibits HCC xenografts in mice in combination with 5-FU. Hepatology 2006;44:205-15. doi: 10.1002/hep.21213.
14. Lu B, Ma Y, Wu G, Tong X, Guo H, Liang A, et al. Methylation of tip30 promoter is associated with poor prognosis in human hepatocellular carcinoma. Clin Cancer Res 2008;14:7405-12. doi: 10.1158/1078-0432.CCR-08-0409.
15. Chen J, Zhu C, Zhu M, Geng M, Tian Y, Li G, et al. Clinicopathologic significance and survival of TIP30 expression in laryngeal squamous cell carcinoma. Int J Clin Exp Med 2015;8:6024-31.
16. Bu F, Liu X, Li J, Chen S, Tong X, Ma C, et al. TGF-β1 induces epigenetic silence of TIP30 to promote tumor metastasis in esophageal carcinoma. Oncotarget 2015;6:2120-33. doi: 10.18632/oncotarget.2940.
17. Chen X, Cao X, Dong W, Luo S, Suo Z, Jin Y, et al. Expression of TIP30 tumor suppressor gene is down-regulated in human colorectal carcinoma. Dig Dis Sci 2010;55:2219-26. doi: 10.1007/s10620-009-0992-0.
18. Tong X, Li K, Luo Z, Lu B, Liu X, Wang T, et al. Decreased TIP30 expression promotes tumor metastasis in lung cancer. Am J Pathol 2009;174:1931-9. doi: 10.2353/ajpath.2009.080846.
19. Guo S, Jing W, Hu X, Zhou X, Liu L, Zhu M, et al. Decreased TIP30 expression predicts poor prognosis in pancreatic cancer patients. Int J Cancer 2014;134:1369-78. doi: 10.1002/ijc.28471.
20. Kononen J, Bubendorf L, Kallioniemi A, Bärlund M, Schraml P, Leighton S, et al. Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 1998;4:844-7. doi: 10.1038/nm0798-844.
21. Jiang C, Ito M, Pierring V, Bruck K, Roeder RG, Xiao H, et al. TIP30 interacts with an estrogen receptor alpha-interacting coactivator CIA and regulates c-myc transcription. J Biol Chem 2004;279:27781-9. doi: 10.1074/jbc.M401832000.
22. King FW, Shitivelman E. Inhibition of nuclear import by the proapoptotic protein CC3. Mol Cell Biol 2004;24:7091-101. doi: 10.1128/MCB.24.16.7091-7101.2004.
23. NicAmhlaibh R, Shitivelman E. Metastasis suppressor CC3 inhibits angiogenic properties of tumor cells in vitro. Oncogene 2001;20:270-5. doi: 10.1038/sj.onc.1204075.
24. Xiao H, Palhan V, Yang Y, Roeder RG. TIP30 has an intrinsic kinase activity required for up-regulation of a subset of apoptotic genes. EMBO J 2000;19:956-63. doi: 10.1093/emboj/19.5.956.
25. Chen V, Shitivelman E. CC3/TIP30 regulates metabolic adaptation of tumor cells to glucose limitation. Cell Cycle 2010;9:4941-53. doi: 10.4161/cc.9.24.14230.
26. Ito M, Jiang C, Krumm K, Zhang X, Pecha J, Zhao J, et al. TIP30 deficiency increases susceptibility to tumorigenesis. Cancer Res 2003;63:8763-7.
27. Li A, Zhang C, Guo X, Liu F, Wang C, Luo R, et al. TIP30 loss enhances cytoplasmic and nuclear EGFR signaling and promotes lung adenocarcinogenesis in mice. Oncogene 2013;32:2273-81,2281e.1-12. doi: 10.1038/onc.2012.253.
28. Pecha J, Ankrapp D, Jiang C, Tang W, Hoshino I, Bruck K, et al. Deletion of tip30 leads to rapid immortalization of murine mammary epithelial cells and ductal hyperplasia in the mammary gland. Oncogene 2007;26:7423-31. doi: 10.1038/sj.onc.1210548.