การแสดงออกของโปรตีน XB130 ในมะเร็งเนื้อเยื่อไต ชนิด papillary

The expression of the XB130 protein in papillary renal cell carcinoma

อรพิน นินทรา[1*] ปิติ อึ้งอารีย์วิทยา[1] สักการ สังฆมานนท์[1] วิเชียร ศิริธนะพล[2] และ จาริญญ์ จินดาประเสริฐ[3]

Orapin Nintra [1*] Piti Ungarreevittaya[1] Sakkarn Sangkhamanon[1] Wichien Sirithanaphol[2] and Jarin Chindaprasirt[3]

[1]ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ขอนแก่น ประเทศไทย

[2]ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ขอนแก่น ประเทศไทย

[3]ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ขอนแก่น ประเทศไทย

[1]Pathologist, Department of pathology, Faculty of Medicine, Khon Khaen University, Khon Khaen, Thailand

[2]Department of Surgery, Srinagarind Hospital, Khon Khaen University, Khon Khaen, Thailand

[3]Department of Medicine, Khon Khaen University, Khon Khaen, Thailand

[*]Corresponding author, E-mail: Orapin_id@hotmail.com

บทคัดย่อ

โปรตีน XB130 เป็นโปรตีนอะแดปเตอร์ เกี่ยวข้องกับวิถี PI3K/Akt ที่ควบคุมการแบ่งตัวเพิ่มจำนวนเซลล์, การอยู่รอดของเซลล์, การควบคุมการแสดงออกของยีน, การเคลื่อนที่และการรุกรานของเซลล์ โปรตีน XB130 มีบทบาทสำคัญในมะเร็งหลายชนิดแต่ยังไม่พบการศึกษาในมะเร็งเนื้อเยื่อไตชนิด papillary การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาการแสดงออกของโปรตีน XB130 ในมะเร็งเนื้อเยื่อไตชนิด papillary กับปัจจัยทางคลินิกทางพยาธิวิทยาและการรอดชีพ โดยทดสอบการแสดงออกของโปรตีน XB130 เนื้อเยื่อพาราฟินบล็อกที่เหลือจากการวินิจฉัยทางพยาธิวิทยาของมะเร็งเนื้อเยื่อไตชนิด papillary จำนวน 24 ราย ตรวจสอบ ด้วยการย้อมอิมมูโนพยาธิวิทยาโดยใช้เทคนิค tissue microarrays พบว่าโปรตีน XB130 มีการแสดงออกต่ำในผู้ป่วย 11 ราย (45.8%) และมีการแสดงออกสูงในผู้ป่วย 13 ราย (54.2%) การแสดงออกที่สูงขึ้นของโปรตีน XB130 สัมพันธ์กับการพยากรณ์โรคที่ไม่ดี (log-rank test, P=0.001) และมีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติกับระดับของรูปร่างนิวเคลียสตามระบบ WHO/ISUP (P=0.006), การแพร่กระจายสู่หลอดน้ำเหลืองหรือหลอดเลือด (P=0.001), การแพร่กระจายไปอวัยวะอื่น (P=0.041), ระยะของมะเร็ง (P=0.004), การเปลี่ยนแปลงของเซลล์เป็นลักษณะ sarcomatoid และ rhabdoid (P=0.012) และการแพร่กระจายสู่ระบบปัสสาวะ (P=0.015) การวิเคราะห์ univariate พบว่าการแพร่กระจายสู่หลอดน้ำเหลืองหรือหลอดเลือด (P=0.038), ระยะของมะเร็ง (P=0.044) และการเปลี่ยนแปลงของเซลล์เป็นลักษณะ sarcomatoid และ rhabdoid (P=0.044) และการแสดงออกสูงของโปรตีน XB130 (P=0.038) เป็น independent prognostic factors การวิเคราะห์ multivariate พบว่าเกี่ยวข้องกับระยะของมะเร็ง (P=0.042) และการแสดงออกสูงของโปรตีน XB130 (P=0.037) เป็น independent risk factors ต่ออัตราการเสียชีวิต

คำสำคัญ: *โปรตีน XB130, มะเร็งเนื้อเยื่อไตชนิด papillary, อัตราการรอดชีพ*

Abstract

XB130 is an adaptor protein, involved the PI3K/Akt pathway, regulated cell proliferation, cell survival, gene regulation, and cell migration and invasion. XB130 plays an important role in many cancers, however, the expression of XB130 protein in papillary renal cell carcinoma (pRCC) has not been investigated. This study aims to determine the correlation between the expression of XB130 with the clinicopathological factors and survival outcomes in pRCC patients. A retrospective study of 24 tissue samples of pRCC from leftover formalin-fixed paraffin embedded tissue (FFPE) to detect XB130 protein expression in pRCC was performed by immunohistochemistry using tissue microarray (TMA) technique. The XB130 protein was an expression in pRCC cells was found weakly expressed in 11 cases (45.8%) and strongly expressed in 13 cases (54.2%). The elevation of XB130 in pRCC tissue was correlated with poorer prognosis in pRCC patients (log-rank test, *P*=0.001). The high XB130 expression was correlated with WHO/ISUP nuclear grade (*P*=0.006), lymphovascular invasion (*P*=0.001), distant metastasis (*P*=0.041), clinical stage (*P*=0.004), sarcomatoid/rhabdoid differentiation (*P*=0.012), and urinary collecting system invasion (*P*=0.015). Univariate analysis showed that lymphovascular invasion (*P*=0.038), clinical stage (*P*=0.044), sarcomatoid/rhabdoid differentiation (*P*=0.044), and high XB130 expression (*P*=0.038) were independent prognostic factors. Multivariate analysis showed that advanced stage (stage III-IV) (*P*=0.042) and high XB130 expression (*P*=0.037) were independent poor prognostic factors and have potential as a novel biomarker for prognosis the XB130 expression in pRCC patients in the future.

Keywords: *XB130 protein, papillary renal cell carcinoma, survival rate*

1. Introduction

XB130 protein is an actin-filament associated protein 1 like 2, which involved cell proliferation, cell survival, gene regulation, cell migration, and tumorigenesis (Shiozaki et al., 2012). It was discovered during the cloning process of human actin-filament associated protein *(hAFAP)* gene with a molecular size of 130 kDa (Xu et al., 2007). The XB130 encodes 818 amino acid proteins and locates on the chromosome 10q25.3. The XB130 has identified as an adaptor protein, the distribution of XB130 in the cytoplasm. It plays a key role in the PI3K/Akt pathway. It can be associated with linked multiple signal molecules that activated lead to signal transduction (Shiozaki & Liu, 2011). XB130 protein is a substrate of several protein tyrosine kinases. These proteins were capable of binding with a p85α subunit of phosphatidylinositol-3-kinase (PI3K) and had effects to activate of Akt and regulate PI3K downstream signaling which is crucial in cancer cells (Bai et al., 2014). In human thyroid cancer, the XB130 regulated cell cycle progression from G1 to S phase and cell survival (Shiozaki et al., 2011). The XB130 induced the Akt-activated phosphorylated to procaspase-8 and procaspase-9, preventing its cleavage into the pro-apoptotic caspase-8 and caspase-9 and decreasing caspase-8 and caspase-9, which are essential steps for extrinsic and intrinsic pathways of cell death, respectively (Tang et al., 2008). Down-regulation

of XB130 decreased cell cycle progression and increased thyroid cancer cell apoptosis (Shiozaki et al., 2011). In cell motility and invasion, with related actin cytoskeleton rearrangement by translocation to the cell periphery in lamellipodia, silencing endogenous XB130 resulting in the decreased rate of wound closure, and inhibited Matrigel invasion (Lodyga et al., 2010). The XB130 is frequently expressed in normal thyroid and spleen (Zhang et al., 2016). Previous research examine XB130 in many tumors, namely, thyroid cancer, ductal breast cancer, prostate cancer, osteosarcoma, and pancreatic ductal adenocarcinoma.

The renal cell carcinoma (RCC) is the most common malignancy of adult kidney cancer, approximately 90%, originated from a renal tubular epithelial cell (Que et al., 2018). The incidence of RCC an occurred about 2% of all cancer and cancer death worldwide. The ratio new diagnosis found that male is more affected than female (2:1) (Hsieh et al., 2017). In Thailand, the prevalence of RCC in the last 5 years is about 1.2% of all cancers. The GLOBOCAN 2018 revealed that the incidence and mortality rate in both sexes and all ages of kidney cancer are accounted for 1.6 cases/100,000 of the population and 0.9 cases/100,000 of the population, respectively and were ranked the 22nd of all cancers (Cancer today Thailand, 2018). The pRCC is the second most common carcinoma accounts for 10-20% of all renal cancers are originated from renal tubular epithelial cells. The pRCC is divided into type 1 and type 2 according to histological morphology where type 2 with prognosis is worse than type 1(Y. Li et al., 2019). Currently, the study of XB130 in papillary renal cell carcinoma has not investigated. Thus, this study aimed to determine the association between XB130 expression in papillary renal cell renal carcinoma with clinicopathological factors, which may lead to being used as a prognosis factor for pRCC in the future.

2. Objectives of the study

The aim of this study was to investigate the association between XB130 expression in papillary renal cell carcinoma tissue, clinicopathological features, and survival outcomes of pRCC patients**.**

3. Materials and methods

3.1 Patient and tissue samples

The study was approved by the Office of the Khon Kean University Ethics Committee in Human Research. The retrospective study has a total of 24 tissue samples obtained from leftover formalin-fixed paraffin embedded tissue (FFPE) of patients from Department of Pathology, Faculty of Medicine, Khon Kaen University who were diagnosed with papillary renal cell carcinoma (pRCC). The patients underwent nephrectomy in the period from January 2007 to August 2017, at Srinagarind Hospital, Khon Kaen University. The clinicopathological data of patients as shown in Table 1. The patients included 18 male (75%) and 6 female (25%) with a mean age of 54.6 ± 15.3 years and age range from 6 -76 years.

3.2 Tissue Microarray (TMAs) constructions

For the tissue microarray, histology H&E slides from each formalin-fixed paraffin embedded samples were review and carefully selected tumor area on the tissue slides by the pathologist, the hemorrhagic and necrotic areas were the exception. The selected areas were representative of the tumor in each FFPE sample used for analysis. For the TMAs created from 24 paraffin-embedded tissue samples of pRCC, TMAs were constructed using the Quick-ray® punch needle (UG06, Unitma, Korea). In each FFPE sample was extracted three tissue cores for representative of tumor region, these cores were defined 3.0 mm in diameter and the procedure has been described in previous studies (Mello et al., 2017; Voduc, Kenney, & Nielsen, 2008). Briefly, punched the tumor area selected from a donor block with TMAs punch needle, then removed extracted tumor core tissue transferred and inserted into a recipient block. Designed the tissue array map of tissue samples with specified a location within TMAs block for each core sample. Human normal kidney used for control.

3.3 Immunohistochemistry stain

The tissue microarray (TMAs) blocks of RCC were sectioned into 3μm, the tissue sections store in a hot air oven to dry overnight at 50°C. Immunohistochemically staining was carried out using the VENTANA Benchmark XT automated slide strainer system (Roche Diagnostics, USA) and detection of XB130 protein expression with ultra-view Universal DAB Detection Kit (Ventana, Roche, USA). An anti-XB130 polyclonal antibody (Abnova, Taiwan) at 1:100 dilution in antibody diluent solution (Biosite, Sweden) following the manufacturer's recommended protocol. For XB130, immunostaining was assessed by two independently of pathologist according to the intensity of stained cells. The interpretation of immunohistochemistry stain can be evaluated Histo score (H-score) by semi-quantitative assessment to assign tumor cell. The cytoplasm staining will be intensity evaluated the intensity levels were scored as 0 (negative), 1+ (weak), 2+ (moderate) or 3+ (strong). The percentage of stained cell in is intensity level, the sum of intensity score from 0 to 300, which calculated the following previous studies (Numata et al., 2012), in the formula:

$$[1\times (\%\ \text{cells}\ 1+) \quad + \quad 2\times (\%\ \text{cells}\ 2+) \quad + \quad 3\times (\%\ \text{cells}\ 3+)]$$

3.4 Statistical Analysis

The correlation between of XB130 protein expression with clinicopathological features was analyzed by $X^2 - Test$ (Chi-square test) and Fisher exact test. Kaplan-Meier method and the log-rank test were used for survival analysis. Cox proportional hazard model using for univariate and multivariate survival analysis, backward stepwise multivariate analysis was performed to find an independent prognostic factor. The statistical analysis was performed using the SPSS 19.0 KKU license software (SPSS, Chicago, IL, USA). Statistical significance was accepted at $P< 0.05$.

4. Results

Expression of XB130 protein in normal kidney and pRCC tissues

The immunohistochemistry analysis of XB130 protein was performed on 24 FFPE of pRCC tissue. In the 11 patients, XB130 protein was the low expression (45.8%) while in another 13 patients, XB130 was the high expression (54.2%). The XB130 protein also expressed in both normal renal tubules and malignancy kidney cancer cells. In normal kidney, XB130 protein was positively expressed in renal tubules and weakly expressed in renal glomerulus (Figure 1B). In pRCC tissue, XB130 protein was a positive expression located specifically on cytoplasm. In contrast, XB130 protein was a negative expression on the nucleus (Figure 1D).

The correlation of XB130 expression with clinicopathological features of pRCC

The expression of XB130 in pRCC tissue was correlated with clinicopathological features of pRCC patients (Table 1). The high expression of XB130 protein was significantly associated with WHO/ISUP nuclear grade (P=0.006), lymphovascular invasion (P=0.001), distant metastasis (P=0.041), clinical stage (P=0.004), sarcomatoid/rhabdoid differentiation (P=0.012), and urinary collecting system invasion (P=0.015), whereas no significant related between XB130 expression with age, gender, tumor laterality, tumor size, lymph node metastasis, and tumor necrosis was found (P<0.05).

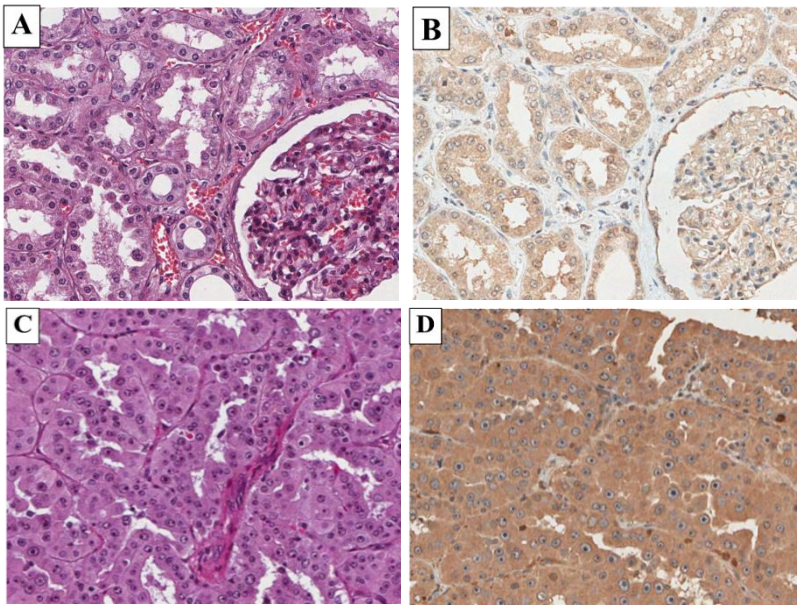

Figure 1 The expression of XB130 in normal kidney tissue and pRCC tissue

A. H&E staining of normal kidney (magnification ×200)

B. IHC staining of normal kidney, the XB130 protein was modulated positive expression in renal epithelial tubular and glomerulus (magnification ×200)

C. H&E staining of pRCC tissue (magnification ×200)

D. IHC staining of pRCC, the XB130 protein was positive expression in cytoplasm of the tumor cell, but negative in the nucleus (magnification ×200)

The association between XB130 protein expression and survival rate of pRCC patients

The Kaplan-Meier survival curves of pRCC patients are shown in Figure 2. The pRCC patients with low XB130 expression group had a longer survival rate and a significantly better prognosis than the high XB130 expression group.

Table 1 The correlation of XB130 protein expression in pRCC tissue with the clinicopathological features

Clinicopathological features	**No. of patients**	**XB130 expression**		***P*-value**
		Low expression n (%)	**High expression n (%)**	
Age (Years)				0.327
< 50	5	1 (20.0)	4 (80.0)	
≥ 50	19	10 (52.6)	9 (47.4)	
Gender				0.813
Male	18	8 (44.4)	10 (55.6)	
Female	6	3 (50.0)	3 (50.0)	
Laterality				0.357
Left	18	7 (38.9)	11 (61.1)	
Right	6	4 (66.7)	2 (33.3)	
WHO/ISUP nuclear grade				**0.006**
Grade I-II	5	5 (100.0)	0 (0.0)	
Grade III-IV	19	6 (31.6)	13 (68.4)	
Tumor size				0.206
< 7 cm	9	6 (66.7)	3 (33.3)	
≥ 7cm	15	5 (33.3)	10 (66.7)	
Lymphovascular invasion				**0.001**
No	11	9 (81.8)	2 (18.2)	
Yes	13	2 (15.4)	11 (84.6)	
Lymph node metastasis				0.223
No	21	11 (52.4)	10 (47.6)	
Yes	3	0 (0.0)	3 (100.0)	
Distance metastasis				**0.041**
No	19	11 (57.9)	8 (42.1)	
Yes	5	0 (0.0)	5 (100.0)	

Clinicopathological features	No. of patients	XB130 expression		*P*-value
		Low expression n (%)	High expression n (%)	
Clinical stage				**0.004**
I-II	12	9 (75.0)	3 (25.0)	
III-IV	12	2 (16.7)	10 (83.3)	
Tumor necrosis				0.408
Absent	14	5 (35.7)	9 (64.3)	
Present	10	6 (60.0)	4 (40.0)	
Sarcomatoid/ Rhabdoid differentiation				**0.012**
No	13	9 (69.2)	4 (30.8)	
Yes	11	2 (18.2)	9 (81.8)	
Urinary collecting system invasion				**0.015**
No	11	8 (72.7)	3 (27.3)	
Yes	13	3 (23.1)	10 (76.9)	

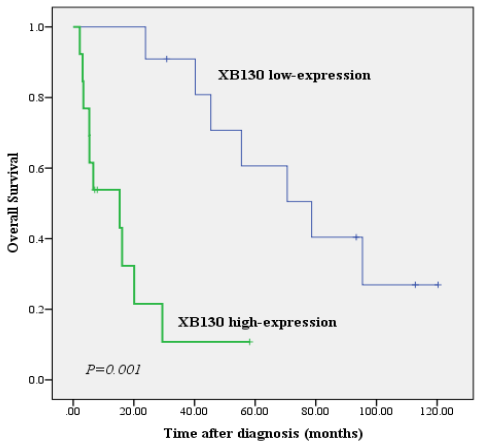

Figure 2 Overall survival of 24 pRCC patients with the expression of XB130 protein.

The Kaplan-Meier survival curves for patients who have diagnosed with pRCC. PRCC patients with low XB130 protein expression had a favorable prognosis than patients with high XB130 expression. The median survival time of pRCC patients with low XB130 protein expression was longer than patients with high XB130 expression (78.7 and 15.3 months, respectively, log-rank test, $P = 0.001$). The findings indicate that pRCC patients with low XB130 protein expression were longer survival than patients with high XB130 expression.

The correlation between XB130 expressions with WHO/ISUP nuclear grade

The XB130 expression is related to nuclear grade of pRCC. The criteria of the nuclear grade according to WHO/ISUP grade are used in this study. In Grade I, nuclei were invisible in both magnification at ×400 and ×100

while nuclear is lymphocyte-like. In Grade II at high power field (×400), the nuclei are prominent but at ×100, the nuclei are inconspicuous. While in Grade III, the nuclei are predominant in both magnification at ×400 and ×100. Lastly, in Grade IV with large nuclear polymorphism, pRCC has a multinuclear giant cell and rhabdoid/sarcomatoid differentiation. The pRCC can be divided into two types, namely, type 1 and type 2. The pRCC type 1, tumor displayed small cuboidal cells, is arranged in a single layer of tumor cells with scant pale cytoplasm and contains foamy histiocytes (Figure 3A). On the other hand, type 2 of pRCC has a pseudostratified layer of tumor cells with abundant eosinophilic cytoplasm and large nuclear (Figure 3C). In the low grade of both types, XB130 protein has a weak expression in type 1 (Figure 3B) and a modulated expression in type 2 of pRCC (Figure 3D) when compared to the high grade of pRCC (Figure 4B, 4D).

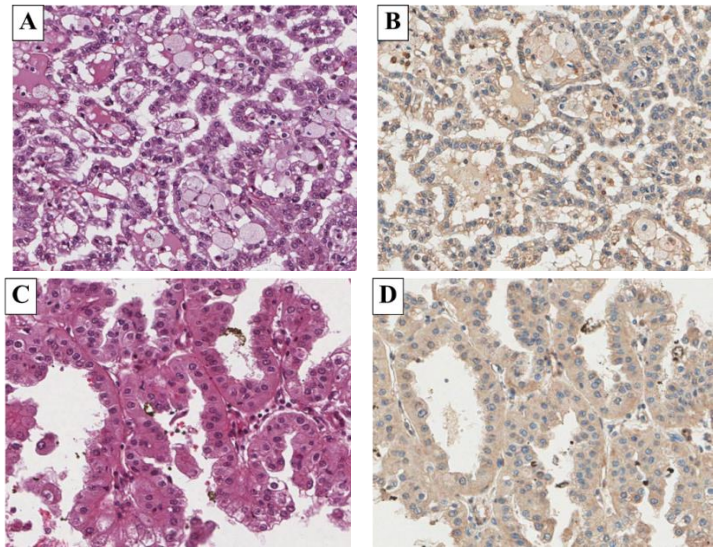

Figure 3 Immunohistochemistry staining (IHC), the expression of XB130 in 2 types of pRCC tissue, grade II

A. The pRCC type 1, H&E staining (×200)

B. IHC staining, the XB130 protein was weakly expression in type 1 of pRCC (×200)

C. The pRCC type 2, H&E staining (×200)

D. IHC staining, the XB130 protein was modulated expression in type 2 of pRCC (×200)

Grade IV of pRCC was associated with sarcomatoid and rhabdoid differentiation which are specific features of nuclear Grade IV of RCC. The sarcomatoid changes and pleomorphic spindle cells are mostly shown in high grade (Figure 4A) in which pRCC with rhabdoid differentiation had large eccentric nuclei, macro nucleoli, and predominant acidophilic globular cytoplasm (Figure 4C). The increased XB130 protein expression was significantly correlated in a high grade of pRCC (Figure 4B, 4D).

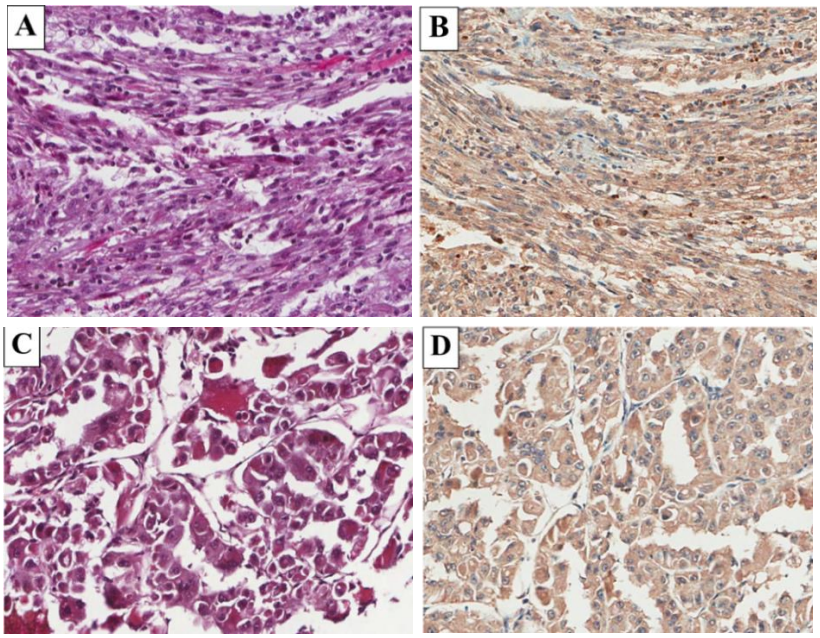

Figure 4 Immunohistochemistry staining, the expression of XB130 in grade IV of pRCC tissue

A. H&E staining, sarcomatoid differentiation (×200)

B. IHC staining, the XB130 protein was strong expression in sarcomatoid differentiation cell (×200)

C. H&E staining, rhabdoid differentiation (×200)

D. IHC staining, the XB130 protein was strong expression in rhabdoid differentiation cell (×200)

Cox's proportional hazard model of prognostic factors

Univariate analysis showed that lymphovascular invasion (*P*=0.038), clinical stage (*P*=0.044), sarcomatoid/rhabdoid differentiation (*P*=0.044), and high XB130 expression (*P*=0.038) were independent prognostic factors in pRCC patients (Table 2). Multivariate analysis showed that pRCC patients with advanced stage (stage III-IV) (*P*=0.042) and high XB130 expression (*P*=0.037) were independent poor prognostic factors. Further, there is a higher risk than pRCC patients lower tumor stage (stage I-II) and low XB130 expression (Table 3).

Table 2 Univariate analysis of prognosis factors in 24 cases of pRCC

Variables	Hazard ratio	95% Confidence interval	*P*-value
WHO/ISUP grade			0.273
Grade I-II	1		
Grade III-IV	3.358	0.384 – 29.346	
Lymphovascular invasion			**0.038**
No	1		
Yes	10.411	1.134 – 95.542	

Variables	Hazard ratio	95% Confidence interval	*P*-value
Distance metastasis			0.417
No	1		
Yes	2.561	0.265 – 24.791	
Clinical stage			**0.044**
Stage I-II	1		
Stage III-IV	10.641	1.061 – 106.712	
Sarcomatoid / Rhabdoid differentiation			**0.044**
No	1		
Yes	9.538	1.060 – 85.826	
Urinary collecting system invasion			0.094
No	1		
Yes	6.639	0.725 – 60.758	
XB130 expression			**0.038**
Low	1		
High	10.411	1.134 – 95.542	

Table 3 Multivariate analysis of prognosis factors in 24 cases of pRCC

Variables	Hazard ratio	95% Confidence interval	*P*-value
Lymphovascular invasion			0.735
No	1		
Yes	1.982	0.038 – 103.614	
Clinical stage			**0.042**
Stage I-II	1		
Stage III-IV	13.902	1.103 – 175.175	
Sarcomatoid/Rhabdoid differentiation			0.184
No	1		
Yes	5.079	0.463 – 55.750	
XB130 expression			**0.037**
Low	1		
High	12.656	1.162 – 137.869	

5. Discussion

XB130 protein plays an important role in the cell proliferation induce cell cycle progression from G1 to S phase, anti-cell apoptosis cause to cell survival, and cell migration and invasion (Shiozaki et al., 2012). The previous studies that examined the XB130 expression in many cancers can detect the expression of XB130 protein in those tumor tissues by IHC stain. The role of XB130 in cancer tissue reveals that high XB130 expression and distant metastasis was a significant independent risk factor for pancreatic ductal adenocarcinoma and that XB130 is a biological indicator of tumor aggressive for the PDAC that is associated with angiogenesis and cell proliferation. The

overexpression of XB130 enhances cell invasiveness and cell motility, resulting in predicted poor survival outcome in PDAC patients (Zhang, Jiang, & Zhang, 2014). The increased expression level of XB130 has involved breast tumorigenesis. The patients with positive XB130 expression in breast cancer tissue are associated with poor prognosis in both cumulative of overall survival and recurrence-free survival compared to patients with negative XB130 expression (J. Li et al., 2015). Similarly, the high XB130 expression was an independent poor prognosis factor for osteosarcoma patients. The OS patients with XB130 positive expression had a significantly poorer 5-year overall and DFS survival than the XB130 negative expression group (Wang et al., 2015). This study aimed to evaluate the expression of XB130 protein in pRCC tissue. The elevated expression level of XB130 in renal cancer tissue was associated with poor prognosis of pRCC patients with a survival time shorter than a group of pRCC patients with XB130 low expression. The results showed that patients with low XB130 expression are 45.8% of pRCC. The XB130 abatement has a correlation significance with a better prognosis than patients with high XB130 expression. The patients with low XB130 expression that correlated to low nuclear grade (I-II) and did not show sarcomatoid/rhabdoid morphological changes are associated with least tumor aggressive than high grade and low risk of postoperative recurrence. Consequently, the patients had a better prognosis. Thus, the WHO/ISUP nuclear grade has used to predict the biological tumor aggressive and metastasis of ccRCC and pRCC (Ishigami et al., 2014). Although the WHO/ISUP nuclear grade had a correlation with XB130 protein expression, no significant prognostic factor for pRCC patients is shown in the univariate and multivariate analysis. The sarcomatoid pRCC has related to low overall survival, tumor aggressive, and progress to rapidly, resulting in patients had poor prognosis resembling sarcomatoid change (Liang et al., 2018). Down-regulation of XB130 expression in follicular thyroid carcinoma inhibited cell cycle progression from G1 to S phase and induced cells apoptosis (Shiozaki et al., 2012). The reduced levels of XB130 expression are involved in decreased tumor cell proliferation in gastric cancer, knockdown GC cells with shXB130 affected to reduce tumor growth. Tumor mass was significantly smaller than GC with XB130 group. In addition, down-regulation of XB130 is related to an increase in E-cadherin the marker of epithelial and decrease in vimentin the marker of mesenchymal, resulting in a reducing of the motility and invasiveness in GC cells (Shi et al., 2014). However, cancer did not spread into the lymphovascular system and the urinary collecting system resulting in pRCC patients' better outcome and tumors non-aggressiveness. In the patients with the tumor in the early-stage, the cancer cell neither spread into lymph nodes nor extend into the other organs. These clinicopathological features were the significant factors that result in good prognosis when compared with high XB130 expression group who had tumor aggressive appearance.

The previous study, there are also studies the XB130 in cancer in both vivo and in vitro. In this study, were performed by IHC staining only in FFPE, but it essential into studies the histologic of pathology. Is the first step into detection the XB130 protein in renal cancer tissue. Furthermore, maybe more investigate the XB130 expression in pRCC fresh tissue in molecular biology and the influence of molecular factor. To be guidance for studies, in the future.

6. Conclusion

In conclusion, the IHC study of XB130 protein expression in 24 pRCC tissue was presented. The XB130 protein is the positive expression in both normal renal epithelial cell and papillary renal cell carcinoma tissue. The level of expression of XB130 protein has a relationship with the survival of pRCC patients. The patients with high XB130 expression had a poorer prognosis and shorter survival time than patients with low XB130 expression. The advanced clinical stage and high expression of XB130 are associated with poor prognosis in which the high XB130 expression is an independent risk for overall survival of pRCC patients and has potential as a novel biomarker for pRCC patients in the future.

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8. References

Cancer today thailand-fact-sheets.pdf. (n.d.). GLOBOCAN 2018. Retrieved 25 Feb, 2019, from http://gco.iarc.fr/today/data/factsheets/populations/764-thailand-fact-sheets.pdf

Bai, X.-H., Cho, H.-R., Moodley, S., & Liu, M. (2014). XB130—A Novel Adaptor Protein: Gene, Function, and Roles in Tumorigenesis. Scientifica, 2014. Doi: 10.1155/2014/903014

Hsieh, J. J., Purdue, M. P., Signoretti, S., Swanton, C., Albiges, L., Schmidinger, M., Ficarra, V. (2017). Renal cell carcinoma. Nature Reviews. Disease Primers, 3, 17009. Doi: 10.1038/nrdp.2017.9

Ishigami, K., Leite, L. V., Pakalniskis, M. G., Lee, D. K., Holanda, D. G., & Kuehn, D. M. (2014). Tumor grade of clear cell renal cell carcinoma assessed by contrast-enhanced computed tomography. SpringerPlus, 3. doi: 10.1186/2193-1801-3-694

Li, J., Sun, W., Wei, H., Wang, X., Li, H., & Yi, Z. (2015). Expression of XB130 in human ductal breast cancer. International Journal of Clinical and Experimental Pathology, 8(5), 5300–5308.

Li, Y., Qiu, X., Li, W., Yang, Y., Yang, R., Zhao, X., Li, X. (2019). Primary Extrarenal Type 2 Papillary Renal Cell Carcinoma: A Case Report. Urology, 123, e1–e3. doi: 10.1016/j.urology.2018.10.039

Liang, X., Liu, Y., Ran, P., Tang, M., Xu, C., & Zhu, Y. (2018). Sarcomatoid renal cell carcinoma: a case report and literature review. BMC Nephrology, 19(1), 84. doi: 10.1186/s12882-018-0884-7

Lodyga, M., Bai, X., Kapus, A., & Liu, M. (2010). Adaptor protein XB130 is a Rac-controlled component of lamellipodia that regulates cell motility and invasion. Journal of Cell Science, 123(Pt 23), 4156–4169. doi: 10.1242/jcs.071050

Mello, R. B., Silva, M. R. R., Alves, M. T. S., Evison, M. P., Guimarães, M. A., Francisco, R. A., Iwamura, E. S. M. (2017). Tissue Microarray Analysis Applied to Bone Diagenesis. Scientific Reports, 7. doi: 10.1038/srep39987

Numata, M., Morinaga, S., Watanabe, T., Tamagawa, H., Yamamoto, N., Shiozawa, M., Miyagi, Y. (2012). The clinical significance of SWI/SNF complex in pancreatic cancer. International Journal of Oncology, 42. doi: 10.3892/ijo.2012.1723

Que, W., Qiu, H., Cheng, Y., Liu, M., & Wu, C. (2018). PTEN in kidney cancer: A review and meta-analysis. Clinica Chimica Acta, 480, 92–98. doi: 10.1016/j.cca.2018.01.031

Shi, M., Zheng, D., Sun, L., Wang, L., Lin, L., Wu, Y., Liao, W. (2014). XB130 promotes proliferation and invasion of gastric cancer cells. Journal of Translational Medicine, 12, 1. doi: 10.1186/1479-5876-12-1

Shiozaki, A., & Liu, M. (2011). Roles of XB130, a novel adaptor protein, in cancer. Journal of Clinical Bioinformatics, 1, 10. doi: 10.1186/2043-9113-1-10

Shiozaki, A., Lodyga, M., Bai, X.-H., Nadesalingam, J., Oyaizu, T., Winer, D., Liu, M. (2011). XB130, a Novel Adaptor Protein, Promotes Thyroid Tumor Growth. The American Journal of Pathology, 178(1), 391–401. doi: 10.1016/j.ajpath.2010.11.024

Shiozaki, A., Shen-Tu, G., Bai, X., Iitaka, D., De Falco, V., Santoro, M., Liu, M. (2012). XB130 Mediates Cancer Cell Proliferation and Survival through Multiple Signaling Events Downstream of Akt. PLoS ONE, 7(8). doi: 10.1371/journal.pone.0043646

Tang, P. S., Mura, M., Seth, R., & Liu, M. (2008). Acute lung injury and cell death: how many ways can cells die? American Journal of Physiology-Lung Cellular and Molecular Physiology. doi: 10.1152/ajplung.00262.2007

Voduc, D., Kenney, C., & Nielsen, T. O. (2008). Tissue Microarrays in Clinical Oncology. Seminars in Radiation Oncology, 18(2), 89–97. doi: 10.1016/j.semradonc.2007.10.006

Wang, X., Wang, R., Liu, Z., Hao, F., Huang, H., & Guo, W. (2015). XB130 expression in human osteosarcoma: a clinical and experimental study. International Journal of Clinical and Experimental Pathology, 8(3), 2565–2573.

Xu, J., Bai, X.-H., Lodyga, M., Han, B., Xiao, H., Keshavjee, S., Liu, M. (2007). XB130, a novel adaptor protein for signal transduction. The Journal of Biological Chemistry, 282(22), 16401–16412. doi: 10.1074/jbc.M701684200

Zhang, J., Jiang, X., & Zhang, J. (2014). Prognostic significance of XB130 expression in surgically resected pancreatic ductal adenocarcinoma. World Journal of Surgical Oncology, 12, 49. doi: 10.1186/1477-7819-12-49

Zhang, R., Zhang, J., Wu, Q., Meng, F., & Liu, C. (2016). XB130: A novel adaptor protein in cancer signal transduction. *Biomedical Reports*, *4*(3), 300–306. doi: 10.3892/br.2016.588