Int J Clin Exp Pathol 2014;7(11):8105-8111
www.ijcep.com /ISSN:1936-2625/IJCEP0002723

Original Article

Differential expression of MST4, STK25 and PDCD10 between benign prostatic hyperplasia and prostate cancer

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Received September 22, 2014; Accepted November 8, 2014; Epub October 15, 2014; Published November 1, 2014

Abstract: Both benign prostatic hyperplasia (BPH) and prostate cancer (PC) are common diseases for men around the world. Both serine/threonine protein kinase MST4 (MST4) and serine/threonine kinase 25 (STK25) belong to the Ste20-like kinases and interact with programmed cell death 10 (PDCD10) which is closely linked to cancer diseases. To clarify the roles of MST4, STK25 and PDCD10 in prostate carcinogenesis, we examined MST4, STK25 and PDCD10 expression in tissue microarray blocks containing 110 cores of BPH and 160 cores of PC immunohistochemically and evaluated their correlation with clinicopathological findings. MST4 was not expressed in all the BPH cases and expressed in 38.7% of PC cases ($P < 0.0001$). STK25 expression was found in 77.3% of BPH cases and 93.1% of PC cases ($P < 0.0001$). PDCD10 staining was considered weak in 82 (74.5%) and strong in 28 (25.5%) of BPH cases. However, in prostate cancer cases, PDCD10 staining was weak in 95 (59.4%) and strong in 65 (40.6%) ($P < 0.05$). PDCD10 and STK25 immunostaining were associated with age in prostatic hyperplasia cases ($P < 0.05$). The staining intensity for STK25 was significantly greater in Gleason grades 3-5 (47.1% of such cases staining strongly) compared with other grades of prostate cancer (only 26.5% of these cases staining strongly; $P < 0.05$). Our results suggest that MST4, STK25 and PDCD10 are unregulated in prostate cancer and may play roles in prostate tumorigenesis. MST4 may be a helpful marker for identifying prostate cancer.

Keywords: MST4, STK25, PDCD10, benign prostatic hyperplasia, prostate cancer

Introduction

Prostate cancer is the most frequently diagnosed cancer in males [1]. The incidence of prostate cancer is increasing steadily, yet our knowledge of its causes is very limited [2-4]. The previous studies which showed elevated levels of active mitogen-activated protein kinase (MAPK) in high-grade and advanced stage prostate and specimens from the androgen-insensitive tumors implicated that MAPK pathway might be involved in the development of prostate cancers and its androgen-independent growth [5].

Sterile 20 (STE20) serine/threonine protein kinase is first described in Saccharomyces cerevisiae as a mitogen-activated protein kinase (MAP4K) involved in the mating pathway [6]. In mammals, more than 30 members of the STE20 superfamily of kinases have been described. MST4 (serine/threonine protein kinase MST4) and STK25 (serine/threonine protein kinase 25) are members of the GCK group III family of kinases, which are a subset of the Ste20-like kinases. Both of MST4 and STK25 are localized to the Golgi apparatus and specifically activated by binding to the Golgi matrix protein GM130. MST4 is detected to participate in the MAPK signal transduction, which specifically activates MEK/ERK to promote cell growth and transformation [7, 8]. Recent studies have showed that MST4 is involved in prostate *in vivo* tumorigenesis and may signal in an EGFP path-

Table 1. Clinicopathologic characteristics of patients in the TMA dataset

Parameters	BPH	PC
Age (y), range (mean)	21-84 (67)	38-87 (69)
Stage		
1 (%)		18 (11.2)
2 (%)		31 (19.4)
3 (%)		35 (21.9)
4 (%)		43 (26.9)
5 (%)		24 (15)
Missing		9 (5.6)
Total	110	160

way [9]. STK25 translocates from the Golgi to the nucleus upon chemical anoxia and induces apoptotic cell death [10]. STK25 also plays a role in cell migration [11, 12].

Programmed cell death 10 (PDCD10) gene, also named TFAR15 (TF-1 cell apoptosis-related gene 15) and CCM3 (cerebral cavernous malformation 3) was originally cloned in our laboratory [13]. Mutations of PDCD10 are one cause of cerebral cavernous malformations, which are vascular malformations that cause seizures and cerebral hemorrhages. Several reports have indicated that PDCD10 interacts with MST4 and STK25 [14-18]. PDCD10 forms a ternary complex with GCKIII (MST4, STK24, STK25) and Golgi matrix protein GM130 to regulate the Golgi morphology [12, 16, 19]. PDCD10 could advance cell proliferation and transformation by activating the MST4 activity and involve itself in the ERK pathway [17]. PDCD10 stabilizes STK25 to accelerate cell apoptosis under oxidative stress [14]. Increasing evidence indicates that PDCD10 may play a part in the tumor signaling because it is upregulated in many cancer tissues, such as pancreatic adenocarcinomas and colorectal cancer [20-22]. Our previous studies have showed that MST4, STK25 and PDCD10 were expressed in prostate cancer cell line PC-3 and could promote cell growth or apoptosis. However, the expression patterns of the three molecules in human prostate cancer tissues are not clear.

In the present study, we evaluated the expression of MST4, STK25 and PDCD10 in prostatic hyperplasia and prostate cancer by using tissue microarray (TMA) technology. Then, we explored their association with clinicopathologic parameters.

Materials and methods

Experimental specimens

Tissue microarrays were obtained from Chaoying Biotechnology Co. (Shanxi, China).

Antibodies

Monoclonal mouse-antibody against PDCD10 was constructed in our lab [23]; polyclonal rabbit-antibody against MST4 was obtained from Cell Signaling Technology Inc. (Danvers, USA); and monoclonal mouse-antibody against STK-25 (clone 1G6) from Abnova Co. (Taipei, Taiwan).

Immunohistochemistry

Sections were deparaffinized and rehydrated with xylene and a series of grades of alcohol. Epitopes were retrieved by heating in a microwave oven with 10 mM citrate buffer (PH 6.0) or 1 Mm EDTA buffer (PH 8.0) for 10 min, followed by cooling for 1 hr at room temperature. Endogenous peroxidase activity was inhibited by 3% hydrogen peroxide. Unspecific binding was blocked with 10% normal serum (for goat) for 30 min. Sections were incubated with anti-PDCD10, MST4 and STK25 antibodies at 4°C over night. Staining procedures were performed in an automated immunostainer (TechMate 1000; Dako) in accordance with the ChemMate protocol using the biotin ± streptavidin detection system (ChemMate-HRP/DAB; Dako). Afterwards, sections were counterstained in haematoxylin. Primary anti-human antibodies were anti-PDCD10, mouse monoclonal diluted 1:100, anti-MST4, rabbit polyclonal diluted 1:50 and anti-STK25 mouse monoclonal diluted 1:50. The unrelated rabbit IgG and mouse IgG at the same concentration were used as negative controls.

Scores of antibody staining

Cytoplasmic immunoreactivity was scored separately according to staining intensity and graded semi-quantitatively as negative (-), weekly positive (+) and strongly positive (++). Each antibody was evaluated in double-blind fashion.

Statistical analyses

Statistical analyses were performed using SPSS13.0 software. Pearson's χ^2-test or Fisher exact test was used to compare categorical

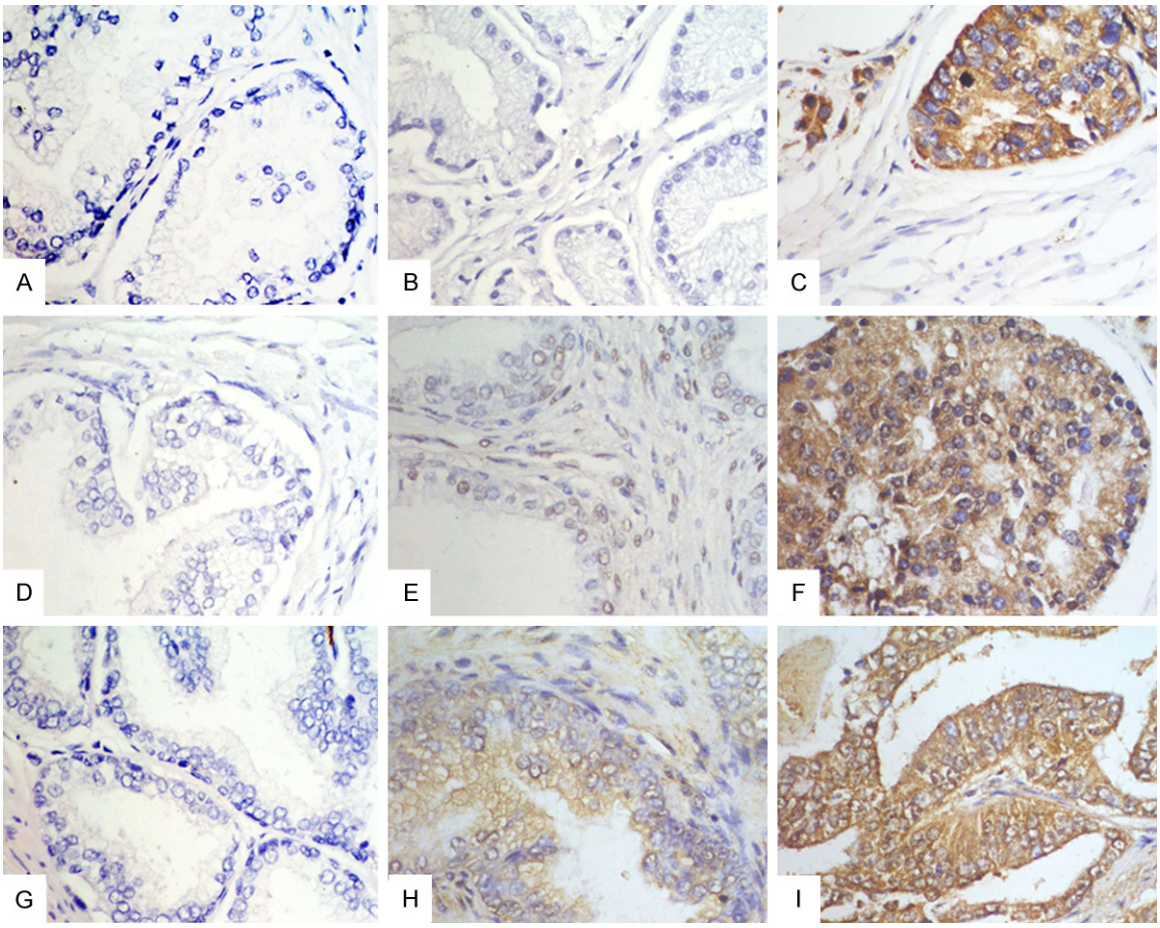

Figure 1. Immunohistochemical analysis of MST4, STK25 and PDCD10 antigen expression in benign prostatic hyperplasia tissues and prostate cancer tissues. A. Negative staining of MST4 in benign prostatic hyperplasia. B. Negative staining of MST4 in prostate cancer. C. Positive staining of MST4 in prostate cancer. D. Negative staining of STK25 in benign prostatic hyperplasia. E. Positive staining of STK25 in prostatic hyperplasia (+). F. Positive staining of STK25 in prostate cancer (++). G. Negative staining of PDCD10 in benign prostatic hyperplasia. H. Positive staining of PDCD10 in prostatic hyperplasia (+). I. Positive staining of PDCD10 in prostate cancer (++). Original magnification × 400.

data. Statistical significance was defined as a *P*-value of < 0.05.

Results

Clinical features of prostatic hyperplasia and prostate cancer

Table 1 demonstrates the clinical and pathologic characteristics of all TMA samples. There were 9 cases of prostate cancer missing the Gleason grade records.

Tissue localization of PDCD10, MST4 and STK25 in the prostate tissue

Representative examples of reactivity for MST4, STK25 and PDCD10 are shown in **Figure 1**. The immunoexpression of them in the benign and the cancerous prostatic epithelium was cytoplasmic. Some cases showed nuclear staining of STK25.

Expression patterns of MST4, STK25 and PDCD10 in prostate specimens by using immunohistochemistry

We did not detect MST4 expression in 110 benign prostatic hyperplasias. MST4 analysis showed positive staining in 38.7% of prostate cancer (**Table 2**). A statistically significant difference in MST4 staining between hyperplasia and cancer tissues was found ($P < 0.0001$).

STK25 was found positive in 77.3% of prostatic hyperplasia and 93.1% in malignant prostate

Table 2. MST4, STK25 and PDCD10 protein expression in benign prostatic hyperplasia and prostate cancer

	MST4		STK25		PDCD10	
	BPH	PC	BPH	PC	BPH	PC
- (%)	110 (100)	98 (61.3)	25 (22.7)	11 (6.9)	0	0
+ (%)	0	62 (38.7)	78 (70.9)	88 (55)	82 (74.5)	95 (59.4)
++ (%)	0	0	7 (6.4)	61 (38.1)	28 (25.5)	65 (40.6)
P value	< .0001		< .0001		.010	

Table 3. Correlation of STK25 and PDCD10 expression with clinicopathologic factor of benign prostatic hyperplasia

Parameters	Total	STK25			PDCD10	
		- (%)	+ (%)	++ (%)	+ (%)	++ (%)
Age	110					
< 65	27	2 (7.4)	22 (81.5)	3 (11.1)	16 (59.3)	11 (40.7)
≥ 65	83	23 (27.7)	56 (67.5)	4 (4.8)	66 (79.5)	17 (20.5)
P value			.039		.036	

cancer (**Table 2**). The frequency of positive cores was significantly higher in cancer tissues than in hyperplasia ($P < 0.0001$).

PDCD10 was expressed in all BPH and PC cases in our study (**Table 2**). PDCD10 staining was considered weak in 82 (74.5%) and strong in 28 (25.5%) of the prostatic hyperplasia cases. In prostate cancer cases, PDCD10 staining was weak in 95 (59.4%) and strong in 65 (40.6%). Hence, the expression of PDCD10 protein was stronger in cancer than hyperplasia ($P = 0.01$).

Clinicopathologic characteristics in association with the intensity of MST4, STK25 and PDCD10 stainings

The correlation between MST4, STK25 and PDCD10 immunoreactivity and several clinicopathologic characteristics was investigated. The TMA had been validated as representative for traditional prognostic variables of prostatic hyperplasia and cancer. These protein expression and clinicopathologic data of the patients are summarized in **Tables 3** and **4**. According to our predefined criteria, both PDCD10 and STK25 immunostaining were associated with age in prostatic hyperplasia cases ($P < 0.05$) (**Table 3**). However, MST4 immunostaining was not associated with age in prostatic hyperplasia. The association between patients' age and MST4, STK25 and PDCD10 expression did not exceed the threshold for statistical significance in prostate cancer ($P > 0.05$) (**Table 4**). In prostate cancer cases, the staining intensity for STK25 was significantly greater in Gleason grades 3-5 (47.1% of such cases staining strongly) compared with other grades of prostate cancer (only 26.5% of these cases staining strongly; $P = 0.04$). The positive MST4 and PDCD10 staining was not associated with Gleason grade in prostate cancer (**Table 4**).

Discussion

In this paper, we examined the expression of MST4, STK25 and PDCD10 and found the three molecules were upregulated in prostate cancer than in benign prostatic hyperplasia, implying that they may play a role in prostate carcinoma progression.

The results presented here suggest that the MST4 is expressed in a higher level in prostate cancer than in benign prostatic hyperplasia, which is consistent with previous reports focused on cell level. Sung, *et al* detected higher expression levels of MST4 in prostate cancer cell lines DU145 and PC-3 than in normal cell lines [9]. The experiments demonstrated that the over expression of MST4 could promote cell growth by specifically activating the ERK pathway [8, 9, 17]. The ERK pathway functions in cellular proliferation, differentiation and survival. Its inappropriate activation is a common occurrence in human cancers. It may be the role that MST4 plays in prostate cancer progression [9]. Our data indicate MST4 as a potential marker or prospective target for the most aggressive forms of prostate carcinoma.

The mammalian kinase STK25 is another member of GCKIII kinases. STK25 can be activated by oxidative stress and induce apoptotic cell death, suggesting STK25 is an important mediator of oxidant-mediated signal transduction [10, 24]. In prostate cancer, oxidative stress, an innate key event characterized by supraphysiological ROS concentrations, has been identified as one of the hallmarks of the aggressive disease phenotype [25]. Specifically, oxidative

Table 4. Correlation of MST4, STK25 and PDCD10 expression with clinicopathologic factors of prostate cancer

Parameters	Total	MST4		STK25			PDCD10	
		- (%)	+ (%)	- (%)	+ (%)	++ (%)	+ (%)	++ (%)
Age	160							
<65	50	28 (56)	22 (44)	6 (12)	27 (54)	17 (34)	34 (68)	16 (32)
≥65	110	70 (63.6)	40 (36.4)	5 (4.5)	61 (55.5)	44 (40)	61 (55.5)	49 (44.5)
P value		.358			.228		.134	
Stage	151							
1-2	49	35 (71.4)	14 (28.6)	3 (6.1)	33 (67.4)	13 (26.5)	31 (63.3)	18 (36.7)
3-5	102	58 (56.9)	44 (43.1)	6 (5.8)	48 (47.1)	48 (47.1)	60 (58.8)	42 (41.2)
P value		.085			.040		.602	

stress is associated with prostate cancer development, progression and response to therapy [26]. Nevertheless, a thorough understanding of the relationships between oxidative stress, redox homeostasis and the activation of proliferation and survival pathways in healthy and malignant prostate remains elusive [25]. Our date showed a significant difference of STK25 expression level between prostate hyperplasia and cancer, while STK25 expression was associated with age in prostate cancer, implying STK25 may play a role in prostate cancer progression. More studies need to be conducted in order to confirm the function of STK25 in tumorigenesis.

Our study provides a new insight into the clinical relevance of PDCD10 in prostate cancer. The mutations of CCM1, CCM2 and PDCD10 gene occur in familial cerebral cavernous malformations, a condition associated with seizures and strokes [27, 28]. Both CCM1 and CCM2 are in a complex which involves in p38 MAPK and integrin signaling pathways [29]. PDCD10 is demonstrated to interact with CCM2 *in vitro* and may function as a stabilizing molecular link between CCM1 and CCM2 [18]. The PP2A phosphatase high-density interaction network defined a large molecular assembly (STRIPAK) that links the PDCD10 and associated GCK-III kinases to a PP2A•striatin•Mob3•STRIP complex [30]. Katrin, *et al* identified that STK25 could phosphorylate PDCD10 [18]. Our previous studies showed that PDCD10 could promote PC-3 cell growth and transformation and exerted its effect through interaction with MST4, via modulation of the ERK pathway, by increasing the activated form of ERK [17]. PDCD10 also interacted with and stabilized STK25 to accelerate cell apoptosis under oxidative stress [14]. Programmed cell death 10 enhances proliferation and protects malignant T cells from apoptosis [31]. Based on all these findings we hypothesized that PDCD10 may be involved in prostate cancer progression. In our experiment, we did observe that difference of PDCD10 expression levels between benign and malignant prostate tissues. PDCD10 is expressed in almost all tissues of which the expression in normal level may play an important role in preserving health. When PDCD10 is expressed in an abnormally high level, it may contribute to tumorigenesis.

In summary, our study showed increased protein expressions of MST4, STK25 and PDCD10 in prostate cancer for the first time, indicating that they may play a role in prostate cancer progression or at least reflect a stage of carcinoma progression. Our data suggest that MST4 may be a novel biomarker for identifying prostate cancer from prostatic hyperplasia.

Acknowledgements

This work was supported the National Natural Science Foundation of China (grant numbers 30872940 and 81300894). The authors thank Ms. Zhang Zirong for assistance with immunohistochemical staining.

Disclosure of conflict of interest

None.

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