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RESEARCH

Correlation Analysis of JAK-STAT Pathway Components on Prognosis of Patients with Prostate Cancer

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Abstract Janus kinases (JAK)/signal transducers and activator of transcription (STAT) pathway is activated constitutively in prostate cancer (PCa). Despite previous reports implying a role of this pathway in the development of clinical hormone-refractory PCa, the correlation of pathway members with the clinicopathologic features and prognosis of patients with PCa has not been elucidated. To address this problem, pJAK-1$^{Tyr1022/1023}$ and pSTAT-3^{Tyr705} were evaluated by immunostaining in needle biopsies of the prostate from 202 PCa patients treated by definitive therapy (105 cases) or hormonal therapy (97 cases). The correlation of two protein expression with the clinicopathologic features and the prognosis of PCa were subsequently assessed. The expression levels of pJAK-1$^{Tyr1022/1023}$ and pSTAT-3^{Tyr705} were both positively correlated with Gleason score and clinical stage of patients with PCa. Their expression was also significantly higher in patients with biochemical (prostate-specific antigen, PSA) failure than that in those with no PSA failure (both $P<0.001$). In all patients, the recurrence-free survival (RFS) rates were significantly higher in those with low pJAK-1$^{Tyr1022/1023}$ and pSTAT-3^{Tyr705} expression than that in those with high expression (both $P<0.001$). Moreover, for patients treated by definitive or hormonal therapy, the RFS rates in those with lower pJAK-1$^{Tyr1022/1023}$ ($P<0.001$ and 0.012, respectively) and pSTAT-3^{Tyr705} expression ($P<0.001$ and 0.015, respectively) were significantly higher than in those with higher expression. Cox multivariate analysis showed that the expression levels of pJAK-1$^{Tyr1022/1023}$ ($P=0.002$) and pSTAT-3^{Tyr705} ($P=0.005$) were prognostic factors for PCa in addition to extraprostatic extension ($P=0.026$) and Gleason score ($P=0.018$). The results of pJAK-1$^{Tyr1022/1023}$ and pSTAT-3^{Tyr705} immunostainings in needle-biopsy specimens are prognostic factors for PCa.

Keywords Prostate cancer · Janus kinases · Signal transducers and activator of transcription · Clinical pathology · Prognosis

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Introduction

Prostate cancer (PCa), as the leading cancer among men all over the world, is presenting a challenge to urologists, radiologists and oncologists. Although recent advances have been made in diagnosis and treatment of PCa, its incidence is still very high and tends to increase year by year. Several environmental and genetic changes involved in the progression of PCa have been investigated, but the precise mechanisms remain unclear. As we know, PCa is a heterogeneous disease with varying clinical outcomes [1]. For men diagnosed with clinically localized PCa, definitive therapy with radical prostatectomy or external beam radiation therapy offers a high chance of cure [2]. Despite intensive efforts on early detection procedures, a large proportion of PCa patients still present with advanced disease and there is no effective cure for men with advanced disease. Therapy against advanced PCa normally

involves androgen ablation and, although initially effective, this therapy eventually fails, leading to a lethal hormone refractory disease [3]. Therefore, in this context, it is of interest the identification of markers which are obviously correlated with clinical outcome of PCa and can help to recognize patients prone to undergo therapeutic failure.

Janus kinases (JAK)/signal transducers and activator of transcription (STAT) signaling pathway plays an important role in various physiological processes, including immune function, cell growth, differentiation and hematopoiesis [4]. Four mammalian JAK family members (JAK1, JAK2, JAK3 and Tyk2) are known to be critical for cytokine signaling. JAKs are constitutively associated with the intra-cytoplasmic portion of cytokine receptors. Ligand binding to these receptors results in conformational changes that lead to the activation and phosphorylation of the associated JAK [5, 6]. This, in turn, leads to the phosphorylation of the intracytoplasmic portion of the receptor, which then serves as a docking site for STAT monomers. STATs are intracellular proteins that have a dual function as signal transducers and activators of transcription. Seven mammalian STAT proteins (STAT1-4, STAT5a, STAT5b and STAT6) have been discovered [7]. There are at least four different mechanisms by which STAT proteins are activated or phosphorylated: the non-receptor tyrosine kinase-mediated mechanism, the receptor tyrosine kinase-mediated mechanism, the cytokine receptor-mediated mechanism and the G protein-mediated mechanism [8]. Of these, the last two mechanisms necessarily involve the activation of JAK. The activated and phosphorylated JAK (pJAK) activate and phosphorylate the docked STAT monomers. The activated and phosphorylated STAT monomers (pSTAT) dissociate from their docking sites, dimerize, and migrate to the nucleus, where they interact with specific DNA binding elements, thus activating transcription [9, 10].

Recently, accumulating evidence indicates that the activation of JAK/STAT pathway is involved in the oncogenesis of PCa. For example, in 2004, Barton et al found the activated STAT3 in pathology specimens obtained from prostatectomy in the cancerous areas but not in the normal margins. Using two PCa cell lines *in vitro*, they also demonstrated that STAT3-specific inhibitors, rather than JAK-specific inhibitors, should be more useful therapeutically in treating androgen-resistant PCa [11]. Consistent with these findings, Agarwal et al. in 2007 demonstrated that STAT-3 was activated constitutively in PCa cell lines and silibinin which could inhibit the activation of STAT3 induced apoptosis in DU145 cells, suggesting that the disruption of STAT-3 could be an effective approach to control PCa [12]. After the large number of *in vitro* functional reports implying a role of JAK/STAT signaling pathway in PCa progression, Tam and coworkers investigated both the expression levels and activation of the IL-6R/JAK/STAT3 pathway in matched hormone-sensitive and hormone-refractory tumors from the same patient. Their results supported the hypothesis that the IL-6R/JAK1/STAT3 pathway is activated in the progression of hormone-refractory PCa. Cytoplasmic expression of IL-6R and $pSTAT3^{Tyr705}$ are associated with reduced time to biochemical relapse and reduced time to death from hormone relapse respectively, therefore, supporting the strategy for targeting this pathway in hormone-refractory prostate cancer treatments [13]. However, there appears to be little data confirming the correlation of JAK/STAT signaling pathway members with the clinicopathologic features and prognosis of patients with PCa. In the present study, we analyzed immunohistochemically the expression of $pJAK\text{-}1^{Tyr1022/1023}$ and $pSTAT\text{-}3^{Tyr705}$ in prostatic biopsy specimens and evaluated them as prognostic markers.

Materials and Methods

Patients and Tissue Samples

The study was approved by the Research Ethics Committee of the China-America Cancer Research Institute of Guangdong Medical College, China. Informed consent was obtained from all of the patients. All specimens were handled and made anonymous according to the ethical and legal standards.

The present study included 202 patients who were diagnosed with PCa at our hospital between 1996 and 2006. The median (range) age of the men at admission was 71 (49–88) years. PCa was diagnosed by histopathological examination of specimens obtained by transrectal needle biopsy of the prostate. The clinical stage was based on the American Staging System (modified Whitmore-Jewett staging system [14]) using a DRE, TRUS, X-ray, CT, MRI and bone scintigraphy. The age, serum PSA level (measured by immunoenzymatic assay) and clinical stages of the 202 patients are shown in Table 1. Among the men, 105 were treated by radical prostatectomy (75) or radiotherapy (30)

Table 1 Clinical features of 202 patients with PCa

Clinical features (n)	Median (range) or n (%)
Age, years (202)	71 (49~88)
PSA level, ng/mL (202)	20.1 (4.2~5860)
Gleason score	
≤6	92 (45.5)
=7	55 (27.2)
≥8	55 (27.2)
Clinical stage	
T1	36 (17.8)
T2	82 (40.6)
T3	80 (39.6)
T4	4 (2.0)

as a definitive therapy. There was no significant difference in the distribution of stage or Gleason score between those treated by radical prostatectomy or radiotherapy. The other 97 patients were treated with hormonal therapy because of high stage or advanced age. Biopsied specimens were fixed in 10% neutral buffered formalin and routinely embedded in the paraffin; 3 μm sections were cut and stained with haematoxylin, and reviewed by a pathologist to determine the Gleason score, based on the Gleason grading system [15]. Patients were followed up with a periodic evaluation by a DRE, serum PSA level and imaging findings. Recurrence of PCa was defined as an increase in the serum PSA level on three consecutive measurements (PSA failure) or the appearance of new softtissue or metastatic lesions.

Immunohistochemistry Analysis

The specimens were fixed in 10% neutral buffered formalin and subsequently embedded in paraffin. The paraffin-embedded tissues were cut at 3 μm and then deparaffinized with xylene and rehydrated for further H&E or peroxidase (DAB) immunohistochemistry staining employing DAKO EnVision System (Dako Diagnostics, Zug, Switzerland). Following a simple proteolytic digestion and a peroxidase blocking, the sections were then incubated at 4°C overnight with the primary anti-pJAK-1$^{Tyr1022/1023}$ (1:100; $^{\#}$3332; Cell Signaling Technology) and anti-pSTAT-3^{Tyr705} antibody (1:50; $^{\#}$9131, Cell Signaling Technology) in PBS containing 1% bovine serum albumin. After washing, peroxidase labeled polymer and substrate-chromogen were then employed in order to visualize the staining of the interested proteins.

Following a hematoxylin counterstaining, the immunostaining was scored by two independent experienced pathologists, who were blinded to the clinicopathological data and clinical outcomes of the patients. The scores of the two pathologists were compared and any discrepant scores were trained by re-examining the staining by both pathologists to achieve a consensus score. Nuclear expression was observed for pJAK-1, while cytoplasmic/nuclear expression was observed for pSTAT-3. For quantification, six microscopic fields, each with an area of 0.06 mm^2, were selected randomly at ×400 within each sample.

Statistical Analysis

The software of SPSS version13.0 for Windows (SPSS Inc, IL, USA) and SAS 9.1 (SAS Institute, Cary, NC) was used for statistical analysis. Continuous variables were expressed as $\overline{X} \pm s$. Statistical analysis was performed with Fisher's exact test for any 2×2 tables,Pearson χ^2 test for non- 2×2 tables, chi-square trend test (the Log Rank, Mantel-Cox) for ordinal datum, Kaplan-Meier and Cox Regression methods for the question of survival analysis. Differences were considered statistically significant when p was less than 0.05.

Results

Expression and Localization of pJAK-1 and pSTAT-3 in PCa Tissues

pJAK-1 and pSTAT-3 positive cells were detected in all PCa specimens tested (Fig. 1a~b for pJAK-1 positive cells and Fig. 1c~d for pSTAT-3 positive cells). The median (range) numbers of pJAK-1-positive cells (pJAK-1 count) and pSTAT-3-positive cells (pSTAT-3 count) were 28.2 (3.3~78.2) and 26.8 (2.9~76.5), respectively. Of the 202 patients, 110 had a pJAK-1 count of >28.2 and were categorized as having a high level of pJAK-1 expression; the remaining 92 had a pJAK-1 count of <28.2 and were categorized as having a low level of pJAK-1 expression (Fig. 1a~b). Of the 202 patients, 105 had a pSTAT-3 count of >26.8 and were categorized as having a high level of pSTAT-3 expression; the remaining 97 had a pSTAT-3 count of <26.8 and were categorized as having a low level of pSTAT-3 expression (Fig. 1c~d).

Correlation of pJAK-1 and pSTAT-3 Expression with the Clinicopathologic Features of PCa

Correlation of the pJAK-1 and pSTAT-3 counts with various clinicopathologic features are shown in Table 2. Patients with high T stage cancer had higher pJAK-1 (P=0.01) and pSTAT-3 (P=0.012) counts. The pJAK-1 and pSTAT-3 counts were both correlated positively with the Gleason score. Patients with PSA failure had significantly higher pJAK-1 and pSTAT-3 counts than those without (both P<0.001). Patients with a high PSA level (≥20 ng/mL) had higher pJAK-1 and pSTAT-3 counts than those with a low PSA level (<20 ng/mL), but the differences had no significance (both P>0.05).

Prognostic Implications of pJAK-1 and pSTAT-3 Expression in PCa

The mean (range) follow-up was 62.6 (5.0–108.0) months. The RFS rate was significantly higher in those patients with lower pJAK-1 and pSTAT-3 counts than in those with higher pJAK-1 and pSTAT-3 counts (both P<0.001) (Fig. 2a~b). Patients with a high Gleason score (≥8) had a significantly lower RFS rate than those with a low Gleason score (<8; P=0.001; Fig. 2c).

In patients treated by definitive therapy, the RFS rate was significantly higher for those with lower pJAK-1 and

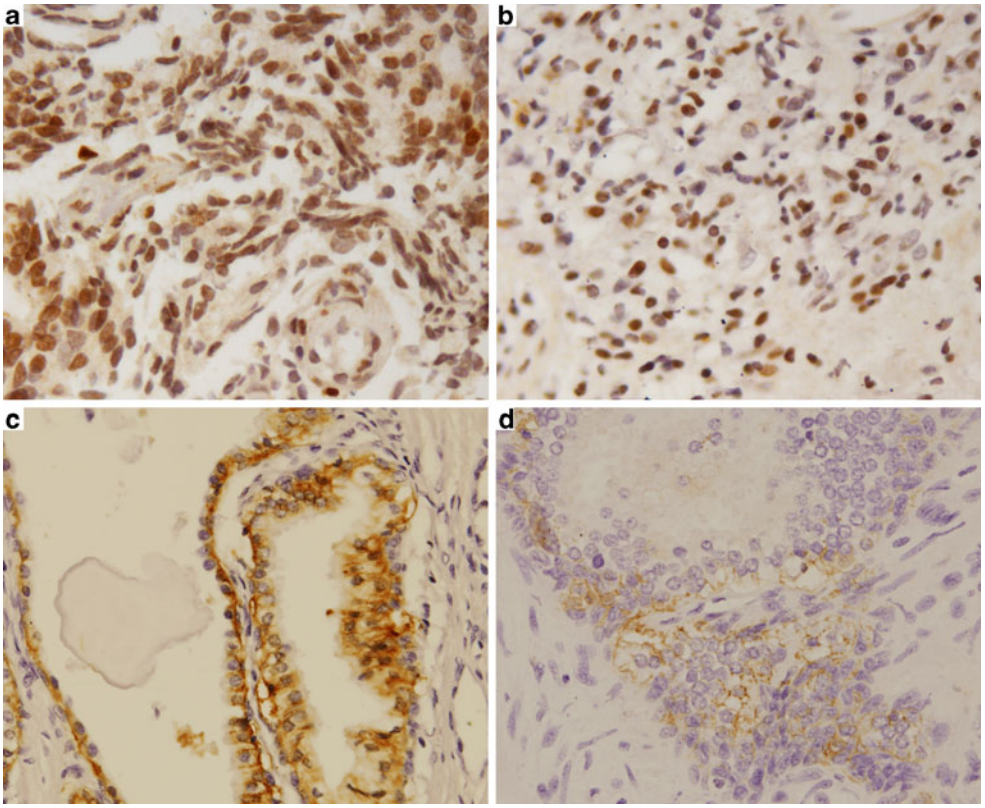

Fig. 1 Immunohistochemical staining for pJAK-1 and pSTAT-3 in PCa (Original magnification × 400). **a**, high pJAK-1 staining; **b**, low pJAK-1 staining; **c**, high pSTAT-3 staining; **d**, low pSTAT-3 staining

pSTAT-3 counts than for those with higher pJAK-1 and pSTAT-3 counts (both $P<0.001$; Fig. 2d~e). Patients with a high Gleason score (≥8) had a significantly lower RFS rate than those with a low Gleason score (<8) ($P=0.01$; Fig. 2f).

In patients treated by hormonal therapy, the RFS rate was lower in those with higher pJAK −1 and pSTAT-3 counts than for those with lower pJAK-1 and pSTAT-3 counts ($P=0.012$ for pJAK −1; $P=0.015$ for pSTAT-3; Fig. 2g~h). Patients with a high Gleason score (≥8) had a significantly lower RFS rate than those with a low Gleason score (<8) ($P=0.02$; Fig. 2i).

Results of multivariate analysis for all patients are shown in Table 3. Cox multivariate analysis showed that the expression levels of pJAK-1 ($P=0.002$) and pSTAT-3 ($P=0.005$) were prognostic factors for PCa in addition to extraprostatic

Table 2 Correlation of the pJAK-1 and pSTAT-3 counts with the clinicopathologic features of PCa

Clinicopathologic features	N (%) of patients	Mean (SEM) pJAK-1 count	p	Mean (SEM) pSTAT-3 count	p
Age, years					
<70	92 (45.5)	27.5 (8.9)	0.3	26.3 (7.5)	0.5
≥70	110 (54.5)	28.8 (9.3)		27.2 (8.2)	
PSA, ng/mL					
≤20	100 (49.5)	27.5 (8.6)	0.3	26.6 (7.9)	0.5
≥20	102 (50.5)	28.9 (9.3)		27.0 (8.2)	
Gleason score					
≤6	92 (45.5)	24.6 (7.8)	0.006*	22.1 (6.3)	0.004*
=7	55 (27.2)	28.3 (8.3)	<0.001**	27.7 (8.6)	<0.001**
≥8	55 (27.2)	34.2 (11.5)	0.001#	33.8 (10.2)	0.001#
Clinical stage					
≤T2	118 (58.4)	25.8 (8.3)	0.01	24.2 (8.0)	0.012
≥T3	84 (41.6)	31.6 (9.2)		30.5 (8.9)	
PSA failure					
+	72 (35.6)	33.9 (10.3)	<0.001	32.1 (9.6)	<0.001
−	130 (64.4)	25.0 (7.5)		23.9 (6.3)	

* ≤6 vs = 7; ** ≤6 vs ≥8; # = 7 vs ≥8

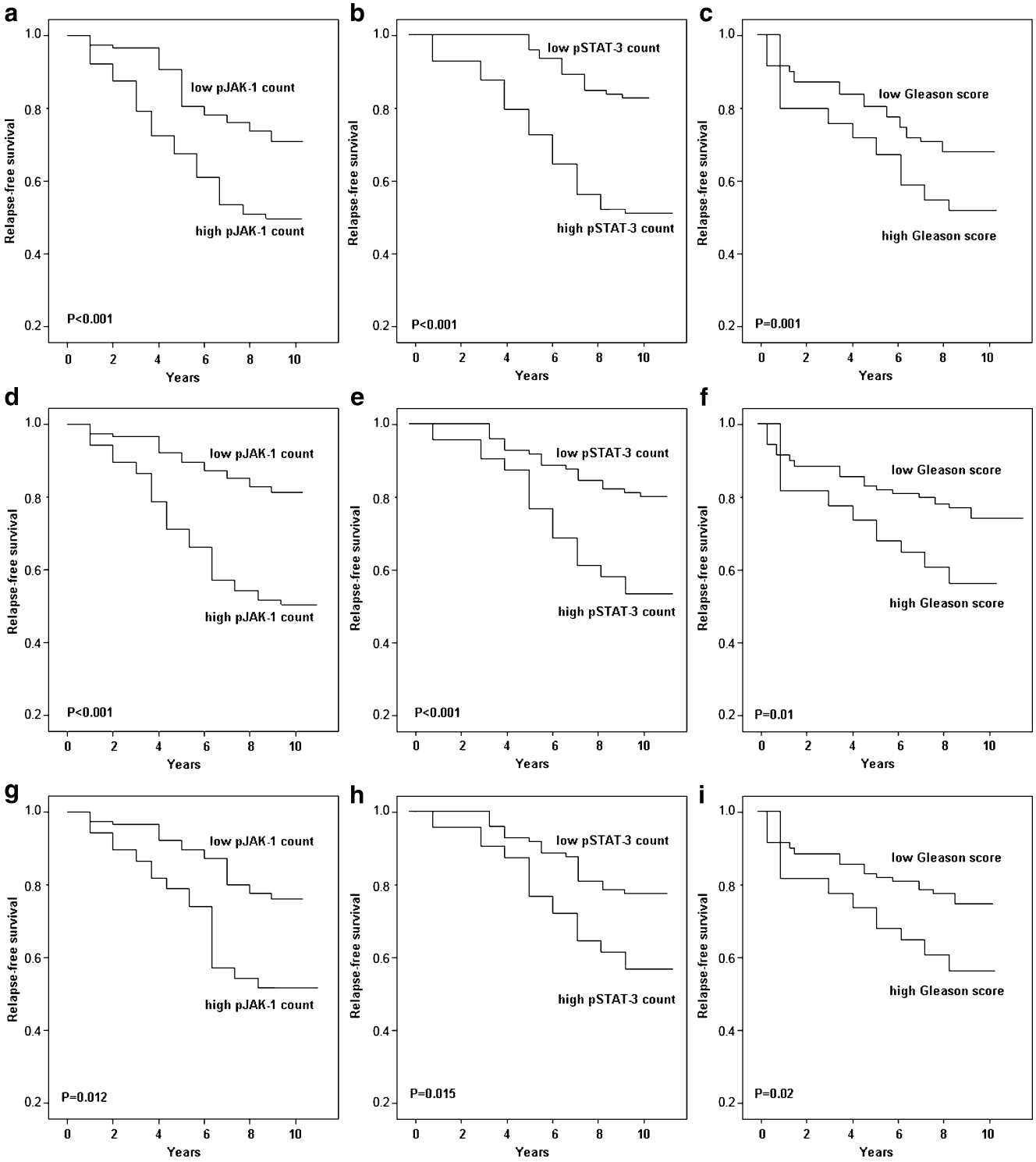

Fig. 2 RFS of patients with PCa: with a high or low pJAK-1 count (**a**), a high or low pSTAT-3 count (**b**) and a high or low Gleason score (**c**); significant differences between groups (a, $P<0.001$; b, $P<0.001$; c, $P=0.001$). RFS of patients with PCa treated by definitive therapy: with a high or low pJAK-1 count (**d**), a high or low pSTAT-3 count (**e**) and a high or low Gleason score (**f**); significant differences between groups (d, $P<0.001$; e, $P<0.001$; f, $P=0.01$). RFS of patients with PCa treated by hormonal therapy: with a high or low pJAK-1 count (**g**), a high or low pSTAT-3 count (**h**) and a high or low Gleason score (**i**); significant differences between groups (g, $P=0.012$; h, $P=0.015$; i, $P=0.02$)

Table 3 Prognostic factors in the Cox multivariate analysis for all patients, those receiving definitive therapy and those treated with hormonal therapy

Prognostic factors	Hazard ratio (95% Cl), P		
	All patients	Definitive therapy	Hormonal therapy
pJAK-1 counts (>28.2)	3.285 (1.569–6.138), 0.002	1.105 (0.982–2.208), 0.01	2.692 (1.576–5.621), 0.008
pSTAT-3 counts (>26.8)	2.989 (1.502–5.998), 0.005	0.982 (0.899–1.896), 0.01	2.058 (1.021–2.006), 0.009
PSA, ng/mL (Continuous vaiable)	1.026 (0.483–2.175), 0.148	0.998 (0.997–1.008), 0.06	1.032 (0.225–2.188), 0.08
Gleason score (>7)	1.962 (1.098–3.276), 0.018	0.582 (0.127–1.859), 0.032	2.628 (1.863–5.231), 0.016
Extraprostatic extension (+)	0.492 (0.116–0.956), 0.026	2.579 (0.889–8.369), 0.018	1.898 (0.996–3.608), 0.053
Lymph node metastasis (+)	0.936 (0.455–1.927), 0.858	–	0.986 (0.107–3.536), 0.831
Distant metastasis (+)	15.60 (2.653–82.661), 0.003	–	33.295 (3.408–133.56), <0.001
DRE (+)	1.004 (0.992–1.016), 0.543	–	0.963 (0.535–2.092), 0.557

extension (P=0.026), distant metastasis (P=0.003) and Gleason score (P=0.018). When Cox multivariate analysis was applied to patients treated by definitive therapy or by hormonal therapy, pJAK −1 (P=0.01 and 0.008) and pSTAT-3 (P=0.01 and 0.009) counts were also significant prognostic factors.

Discussion

PCa is the most commonly occurring cancer in men and advanced PCa is currently incurable. Occidentals had higher morbidity than Chinese, but the morbidity of PCa has risen in China recently [16]. With the number of elderly people increasing in China, China will be a country with high and increasing morbidity for PCa in the future. Because of the limitations in efficient detection techniques, clinicians cannot determine which patients should be treated immediately. Thus, there is a need for further elucidation of the underlying molecular mechanisms of prostate carcinogenesis in order to identify early diagnostic and prognostic markers for PCa. At present, the Gleason score is widely used as the most important pretreatment marker for evaluating the aggressiveness of PCa. However, the variation in the Gleason score may exist among pathologists [17]. Moreover, PSA is the most common indicator used for PCa diagnosis, but its specificity to PCa tissues is not very high. Some benign lesion, such as prostatitis and benign prostate hyperplasia also can lead to elevated PSA [18]. Given these reasons, to find reliable biomarkers that can be available worldwide and which will help to improve the evaluation and prognosis of patients and further stratify patients into different risk groups for whom specific adjuvant therapies may be appropriate is a great challenge to clinicians and basic scientists.

Constitutive activation of JAK/STAT signaling pathway has been detected in a variety of human tumors and cancer cell lines, including blood malignancies and solid tumors. For example, it has been demonstrated that JAK-2 was activated in childhood T cell acute lymphoblastic leukemia [19]. Constitutive activation of STAT-3 correlates with cell proliferation in breast carcinoma and non–small cell lung cancer, and also inhibits apoptosis [20]. Xiong and coworkers revealed by immunohistochemical staining that nuclear staining of phospho-STAT3 mostly presents in adenomas and adenocarcinomas, and a positive correlation was found between phospho-JAK2 immunoreactivity and the differentiation of colorectal adenocarcinomas [21]. Conversely, inhibition of JAK/STAT signaling suppresses cancer cell growth and induces apoptosis in various cancers. Recent studies have also revealed that altered STAT-3 activation can contribute to oncogenesis. For example, activation of STAT-3 is required for cell transformation by oncogenic Src and by a constitutively active form of Gαo, a heterotrimeric G-protein subunit [22]. These published reports all demonstrate the crucial importance of the JAK/STAT pathway in tumorigenesis and progression.

JAK-1 and STAT-3 are proteins that become activated in sequence. STAT-3 is phosphorylated at two different sites, tyrosine 705 and serine 727 [23]. The tyrosine kinase, JAK-1 phosphorylates STAT-3 at tyrosine 705 [24]. Immunohistochemical staining in our cohort of patients has demonstrated that the phosphorylated form of JAK-1 was found in the nuclear compartments of the cell and the phosphorylated form of STAT-3 was found in the cytoplasmic and nuclear compartments of the cell. STAT-3 dimerization occurs in the cytoplasm before it enters the nucleus, the presence of activated STAT-3 in the cytoplasm, therefore, provides a ‘snapshot’ of activated STAT-3 before it enters the nucleus.

In the present study, high expression of pJAK-1 and pSTAT-3 correlated significantly with a high Gleason score and high tumour stage. These findings are consistent with reports showing a correlation of JAK-1/STAT-3 pathway activation in PCa with shorter time to death from

biochemical relapse and poor prognosis of PCa by analysis of surgical specimens [13]. In the present series, the RFS rate was significantly lower for patients with higher pJAK-1 and pSTAT-3 counts and a higher Gleason score than for those with lower pJAK-1 and pSTAT-3 counts and a lower Gleason score when the RFS was assessed for all patients. Similarly, the RFS rate was assessed in patients treated by definitive therapy (radical prostatectomy or radiotherapy); as expected, those with lower pJAK-1 and pSTAT-3 counts had a better RFS rate than those with higher pJAK-1 and pSTAT-3 counts. Multivariate analyses also showed that higher pJAK-1 and pSTAT-3 counts in biopsy specimens were significant prognostic factors, as was the Gleason score. From these data, we can predict PSA failure after definitive and hormonal therapy by the pJAK-1 and pSTAT-3 counts in the prostatic biopsy specimens. Although most patients are currently diagnosed with clinically localized disease, 30–40% fail to respond to local definitive therapy within 10 years, as evidenced by an increase in the PSA level [25]. Hormonal therapy is widely used in clinics, particularly in older patients [26]. The RFS rate was better in patients with a lower pJAK-1 and pSTAT-3 counts than in those with higher pJAK-1 and pSTAT-3 counts. There have been several studies in which multivariate analyses showed the prognostic significance of stage, Gleason score and serum PSA level for PCa. In the present study, the pJAK-1 and pSTAT-3 counts were also significant prognostic indicators for PCa. The present multivariate analysis also showed the pJAK-1 and pSTAT-3 counts to be independent prognostic indicators for RFS. Use of the pJAK-1 and pSTAT-3 counts in biopsy specimens allows a prediction of the prognosis of PCa at the time of diagnosis.

In conclusion, the activation of JAK-1 and STAT-3 may play an important role in the progression of PCa. The expression of pJAK-1 and pSTAT-3 determined by immunohistochemistry is an prognostic indicator for PCa and might be used as an indicator for PSA failure after definitive therapy and for the response to hormonal therapy.

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