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Decreased expression of STAT5A predicts poor prognosis in osteosarcoma

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ABSTRACT

Background: Signal transducer and activator of transcription 5 (STAT5) plays a key role in the malignancy of many tumors and has been identified as a therapeutic target. However, the role of STAT5A in osteosarcoma is still unclear.

Methods: 98 osteosarcoma patients were obtain from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET). The relationship between STAT5A and clinical features was analyzed using the Wilcoxon signed-rank test and logistic regression. Kaplan–Meier method, univariate and multivariate Cox regression analyses were performed to assess the prognostic value in event-free survival (EFS) and overall survival (OS). Gene Set Enrichment Analysis (GSEA) was performed.

Results: STAT5A low expression was not linked to age, gender, tumor site, surgical approach, tumor region, histologic response, and metastasis, but was correlated with progression (OR = 5.2, $P = 0.012$). Kaplan–Meier survival curve showed that patients with STAT5A low expression had worse EFS and OS than those with STAT5A high expression ($P < 0.01$). Furthermore, the multivariate analysis revealed STAT5A was an independent prognostic factor for poor OS (HR = 3.29, $P = 0.0408$)) and EFS (HR = 7.29, $P = 0.0025$). GSEA showed that the complemen, metabolism, apoptosis, interferon-gamma response, inflammatory response, Notch, Kras, reactive oxygen species, VEGF, IL-6/JAK/STAT3, IL-2/Stat5, B-cell receptor, and p53 pathways were significantly associated with the STAT5A gene.

Conclusions: STAT5A may be a novel prognostic factor for osteosarcoma and may act as a molecular target in the treatment of osteosarcoma.

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor that occurs mainly in children and adolescents, with an estimated incidence of 3 cases per million [2,22]. Depending on the success of surgery in combination with chemotherapy, the five-year survival rate has significantly increased to over 60% in patients with localized tumor [6,17]. However, approximately 50% of all patients at the time of diagnosis develop metastases, these patients with metastasis or recurrence have a poor 5-year survival rate of < 20% [13,27]. Thus, the identification of new molecule target is urgently needed to predict the prognosis of osteosarcoma and to improve the treatment of osteosarcoma patients.

The signal transducer and activator of transcription (STAT) family is reported to be possibly activated by inflammatory cytokines or growth factor receptors and is involved in many cellular processes (i.e. cell differentiation, proliferation or growth), apoptosis, immune response, and inflammation [1,3,21]. STAT5, a member of the STAT family, regulates the proliferation and inhibition of apoptosis in cancer cells, and is involved in the self-renewal of hematopoietic stem cells and Fas-mediated cell death [33,35]. STAT5 is linked to tumor progression through induction of epithelial-mesenchymal transition [9]. There are two separate STAT5 proteins, STAT5A and STAT5B. STAT5A might act as a key tumor suppressor gene [39]. The constitutive activation of STAT5A enhances human hematopoietic stem cell self-renewal and erythroid differentiation [24]. STAT5A is required for the development of mammary cancers in mice [23]. STAT5A promotes B-cell responses to cytokines and may contribute to lymphoma and leukemia growth [34]. STAT5A is found to be widely downregulated in some cancers, including cervical cancer [28], breast cancer [18], and chronic myelogenous leukemia [7]. Low expressions of STAT5A was correlated with histological differentiation and poor relapse-free survival in breast cancer [36]. High expression of STAT5A is associated with a favorable overall survival in ovarian cancer [10]. Targeting transcription factor STAT5 may be a potential therapeutic strategy for cancer [8,11]. However, the prognostic role of STAT5A in osteosarcoma has not been studied.

Therefore, the purpose of the current study was to evaluate the

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prognostic significance of STAT5A expression in osteosarcoma. To gain further insight into the biological processes and signaling pathways involved in osteosarcoma pathogenesis related STAT5A regulatory role, GSEA was carried out.

2. Materials and methods

2.1. Patient samples

The mRNA expression profiles (Transcripts Per kilobase Million: TPM values) and corresponding clinical data for patients with osteosarcoma were obtained from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET). Non-tumor samples were lacking. Other datasets such as GSE datasets from the Gene Expression Omnibus (GEO) were not available because of insufficient clinical information. Finally, the gene expression data of 98 cases with osteosarcoma and clinic data were included and further analyzed in this study. The clinical patient information included age, gender, tumor site, tumor region, surgical approach, progression, histologic response, and distant metastasis. Event-free survival (EFS) (progression, relapse, second malignant neoplasm, or death) and overall survival (OS) (death) were estimated. The baseline clinical characteristics are listed in Table 1.

2.2. Gene set enrichment analysis

Gene set enrichment analysis (GSEA) was utilized to explore signaling pathways and biological processes [29]. In this study, the gene sets of "h.all.v6.2.symbols.gmt and c2.cp.kegg.v6.2.symbols.gmt" from the Molecular Signatures Database (MSigDB), the specific well-defined biological states or processes, were analyzed using the GSEA software 3.0. The expression level of the STAT5A gene was used as a phenotype label. GSEA was carried out to investigate the mechanisms related to STAT5A in osteosarcoma. To acquire a normalized enrichment score (NES), the number of gene set permutations was set at 1000 for each analysis. A nominal P-value < 0.05 and a false discovery rate (FDR) < 0.25 were considered to indicate significant enrichment results.

Table 1
Basic characteristics of patients.

Characteristics		Number of cases	%
Age at diagnosis (y)		Median 15.1 (3.6–39.9)	
Gender			
	Male	58	59.2
	Female	40	40.8
Surgical approach			
	Limb sparing	48	87.3
	Amputation	6	10.9
	Limb sparing and amputation	1	1.8
Tumor site			
	Femur	47	69.1
	Tibia	21	30.9
Tumor region			
	Distal	35	56.4
	Proximal	24	38.7
	Other, not specified/ posterior	3	4.8
Progression			
	Yes	18	37.5
	No	30	62.5
Histologic response			
	Poor (necrosis of ≤90%)	34	65.4
	Good (necrosis of > 90%)	18	34.6
Metastasis			
	Yes	24	24.5
	No	74	75.5

2.3. Statistical analysis

STAT5A expression was determined using the median value as the cutoff. The Wilcoxon signed-rank test and univariate logistic regression analysis were utilized to evaluate the relationship between STAT5A expression and clinicopathological features. Kaplan–Meier survival curves with log rank test were used to estimate the correlation between STAT5A expression and EFS and OS. Clinicopathological characteristics and STAT5A expression associated with EFS and OS were calculated using univariate Cox proportional hazard regression analysis. The prognostic results of the univariate Cox analysis with the *P*-values < 0.1 were considered as the candidate variables, multivariate Cox proportional hazard regression analysis was further performed using the candidate prognostic factors (i.e. STAT5A expression, histologic response, and metastasis). Statistical analyses were performed by using R version 3.5.1.

3. Results

3.1. Patient characteristics

As shown in Table 1, Ninety eight patients (58 males and 40 females) with both clinical and gene expression data were obtained in November 2018. The expression of STAT5A was examined in osteosarcoma. The median age at diagnosis was 15.1 years (range 3.6–39.9 years). The distribution of tumor site included femur and tibia, 69.1% of the tumors occurred in the femur and 30.9% in the tibia. 56.4% (n = 35) were distal tumor and 38.7% (n = 24) were proximal tumor. Most tumors (62.5%, n = 30) did not have progression and 37.5% of the tumors had progression. 24 of 98 (24.5%) cases had distant metastases. 18 of 52 (34.6%) cases exhibited a good histologic response. Median follow-up for OS was 37.4 months (range 0–192 months). Median follow-up for EFS was 20 months (range 0–143.8 months).

3.2. Association between STAT5A expression and clinicopathological variables

A total of 98 osteosarcoma patients with STAT5A expression data across all patient characteristics were analyzed. The univariate logistic regression analysis revealed that low expression of STAT5A was not associated with age, gender, tumor site, surgical approach, tumor region, histologic response, and metastasis (all *P* values > 0.05). STAT5A low expression was correlated with progression (yes vs. no: OR = 5.2, 95% CI = 1.44–18.71, $P = 0.012$) (Table 2). Moreover, expression level of STAT5A was significantly associated with progression ($P = 0.0037$) (Fig. 1A).

3.3. Kaplan–Meier survival analysis

Kaplan–Meier curve showed that osteosarcoma with STAT5A low expression had a worse prognosis than that with STAT5A high expression in terms of OS and EFS ($P = 0.0021$ and $P = 0.0023$, respectively)

Table 2
STAT5A expression associated with clinicopathological features.

Factors	Total (N)	OR with 95% CI	*P*
Gender (Male vs. female)	98	0.84 (0.38–1.89)	0.681
Age (≥15.1 years vs. < 15.1 years)	98	0.56 (0.25–1.25)	0.159
Tumor site (Femur vs. Tibia)	68	1.8 (0.64–5.09)	0.268
Tumor region (Distal vs. proximal)	59	0.6 (0.21–1.72)	0.342
Surgery (Limb sparing vs. amputation)	54	5 (0.54–46.05)	0.155
Histologic response (Poor vs. good)	52	0.89 (0.28–2.79)	0.84
Progression (Yes vs. no)	48	5.2 (1.44–18.71)	0.012
Metastasis (Yes vs. no)	98	1.96 (0.76–5.04)	0.162

OR: odds ratio; 95 %CI: 95 % confidence interval.

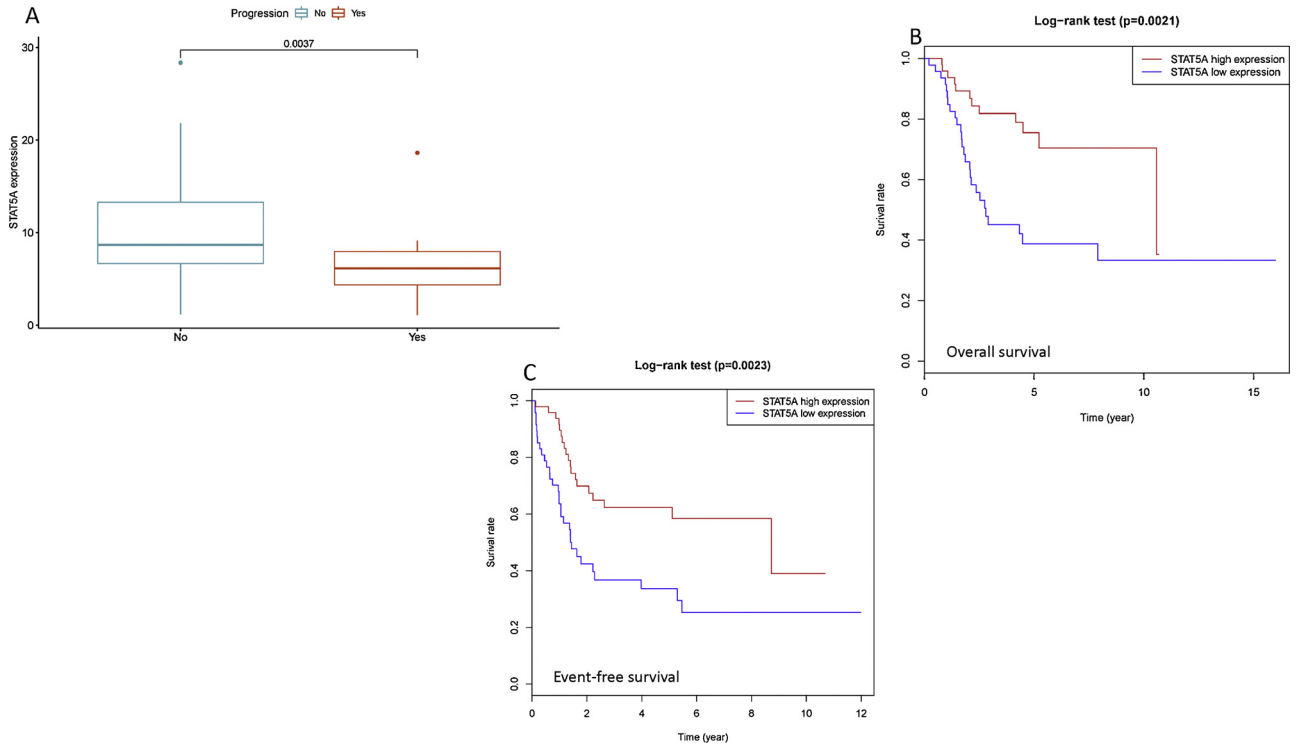

Fig. 1. Correlation between STAT5A expression and clinical prognostic characteristics, including (A) Progression, (B) Impact of STAT5A expression on overall survival, and (C) Impact of STAT5A expression on event-free survival.

(Fig. 1B-C).

3.4. Univariate and multivariate Cox regression analyses

The univariate analysis showed that STAT5A low expression was significantly associated with worse OS (HR = 2.81, 95% CI = 1.42–5.60, $P = 0.0032$), along with histologic response and metastasis (all P values < 0.05). The multivariate analysis further revealed that STAT5A low expression was independently associated with worse OS (HR = 3.29, 95% CI = 1.05–10.32, $P = 0.0408$) (Table 3).

In univariate analysis using Cox proportional-hazard models, STAT5A low expression was significantly correlated with poor EFS (HR = 2.38, 95% CI = 1.34–4.22, $P = 0.0031$). Other clinical variables such as tumor site, tumor region, histologic response, progression, and metastasis were found to have impact on EFS (all P values < 0.05). At multivariate analysis, low expression of STAT5A remained independently associated with poor EFS, with a HR of 7.29 (95% CI = 2.01–26.40, $P = 0.0025$) (Table 4).

Table 3
Univariate and multivariate analyses in overall survival (OS).

Variables	HR with 95% CI	*P*
Univariate analysis		
STAT5A (Low vs. high)	2.81 (1.42–5.60)	0.0032
Gender (Male vs. female)	0.97 (0.51–1.87)	0.931
Age (≥15.1 years vs. < 15.1 years)	0.88 (0.47–1.67)	0.7
Tumor site (Femur vs. Tibia)	2.79 (0.96–8.16)	0.0606
Tumor region (Distal vs. proximal)	2.69 (0.99–7.25)	0.0511
Surgery (Limb sparing vs. amputation)	1.49 (0.35–6.42)	0.591
Histologic response (Poor vs. good)	3.93 (1.16–13.36)	0.0283
Progression (Yes vs. no)	1.84 (0.86–3.92)	0.116
Metastasis (Yes vs. no)	3.81 (1.99–7.29)	< 0.001
Multvariate analysis		
STAT5A (Low vs. high)	3.29 (1.05–10.32)	0.0408
Tumor site (Femur vs. Tibia)	6.52 (0.77–55.19)	0.0852
Histologic response (Poor vs. good)	3.26 (0.66–16.02)	0.1462
Metastasis (Yes vs. no)	3.84 (0.94–15.67)	0.0612

HR: hazard ratio; 95 %CI: 95 % confidence interval.

Table 4
Univariate and multivariate analyses in event-free survival (EFS).

Variables	HR with 95% CI	*P*
Univariate analysis		
STAT5A (Low vs. high)	2.38 (1.34–4.22)	0.0031
Gender (Male vs. female)	1.25 (0.70–2.21)	0.453
Age (≥15.1 years vs. < 15.1 years)	0.67 (0.38–1.17)	0.161
Tumor site (Femur vs. tibia)	2.53 (1.10–5.83)	0.0293
Tumor region (Distal vs. proximal)	2.64 (1.17–5.94)	0.0194
Surgery (Limb sparing vs. amputation)	0.89 (0.31–2.57)	0.827
Histologic response (Poor vs. good)	4.5 (1.55–13.08)	0.0057
Progression (Yes vs. no)	3.41 (1.71–6.81)	0.0005
Metastasis (Yes vs. no)	2.68 (1.50–4.80)	0.0009
Multvariate analysis		
STAT5A (Low vs. high)	7.29 (2.01–26.40)	0.0025
Tumor site (Femur vs. tibia)	5.88 (0.58–59.86)	0.1346
Histologic response (Poor vs. good)	5.42 (0.65–45.17)	0.1186
Progression (Yes vs. no)	5.28 (1.19–23.39)	0.0283
Metastasis (Yes vs. no)	4.40 (0.62–31.27)	0.1387

HR: hazard ratio; 95 %CI: 95 % confidence interval.

3.5. Identification of biological processes and signaling pathways

To identify the biological functions and potential molecular pathways of STAT5A in osteosarcoma progression, we conducted GSEA between high and low expression groups of STAT5A. Figs. 2 and 3 revealed significant results (normal p-value < 0.05 and FDR < 0.25) in enrichment of MSigDB Collection (h.all. and c2.cp.kegg v6.2. symbols). We chose significantly enriched biological process and signaling pathways according to their normalized enrichment score (NES). The results demonstrated that complement (HALLMARK_COMPLEMENT), metabolism (HALLMARK_XENOBIOTIC_METABOLISM and HEME_METABOLISM), apoptosis (HALLMARK_APOPTOSIS), interferon-gamma

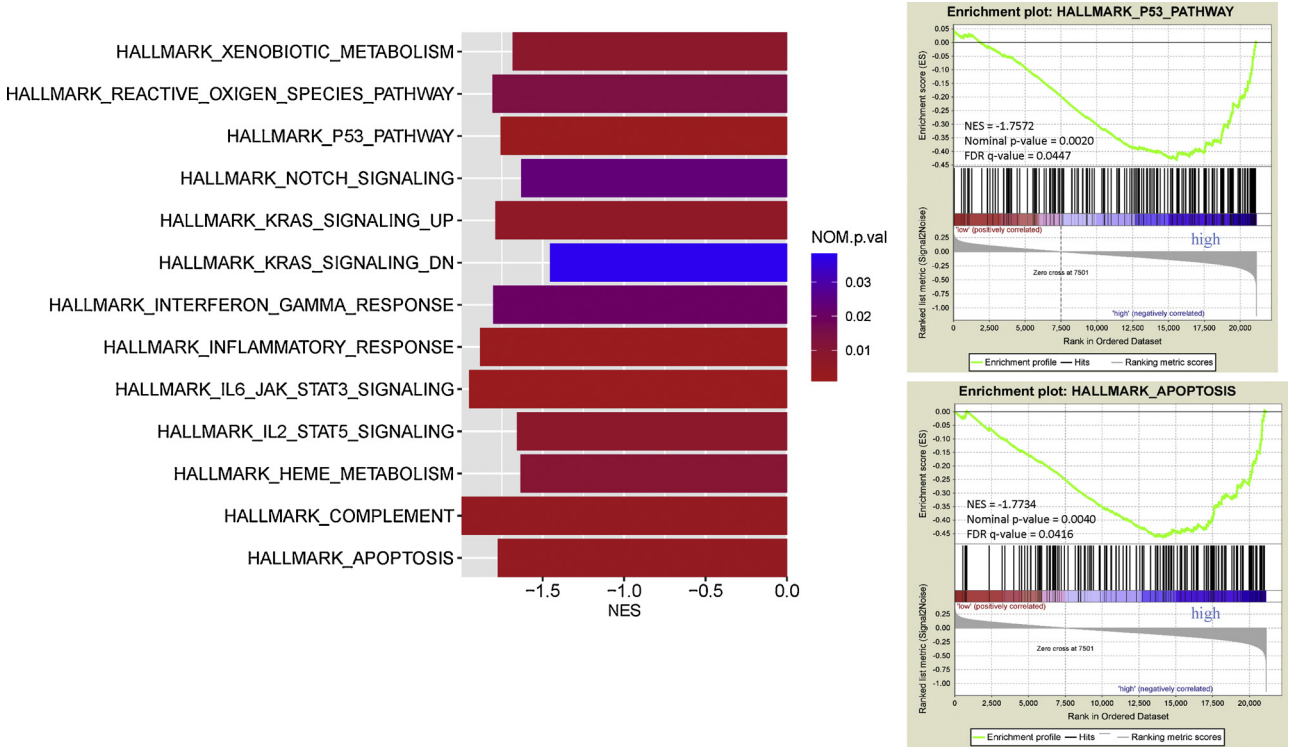

Fig. 2. Enrichment plots from HALLMARK for significant enrichment functions (normal p-value < 0.05 and FDR < 0.25). NES: normalized enrichment score; FDR: false discovery rate.

response (HALLMARK_INTERFERON_GAMMA_RESPONSE), the inflammatory response (HALLMARK_INFLAMMATORY_RESPONSE), as well as Notch (HALLMARK_NOTCH_SIGNALING), Kras (HALLMARK_KRAS_SIGNALING_UP and KRAS_SIGNALING_DN), IL-6/JAK/STAT3 (HALLMARK_IL6_JAK_STAT3_SIGNALING), IL-2/Stat5 (HALLMARK_IL2_STAT5_SIGNALING), reactive oxygen species (HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY), and p53 pathways (HALLMARK_P53_PATHWAY) were significantly enriched in STAT5 A high expression group (Fig. 2). The gene signatures from kegg also showed that many biological processes and signaling pathways such as

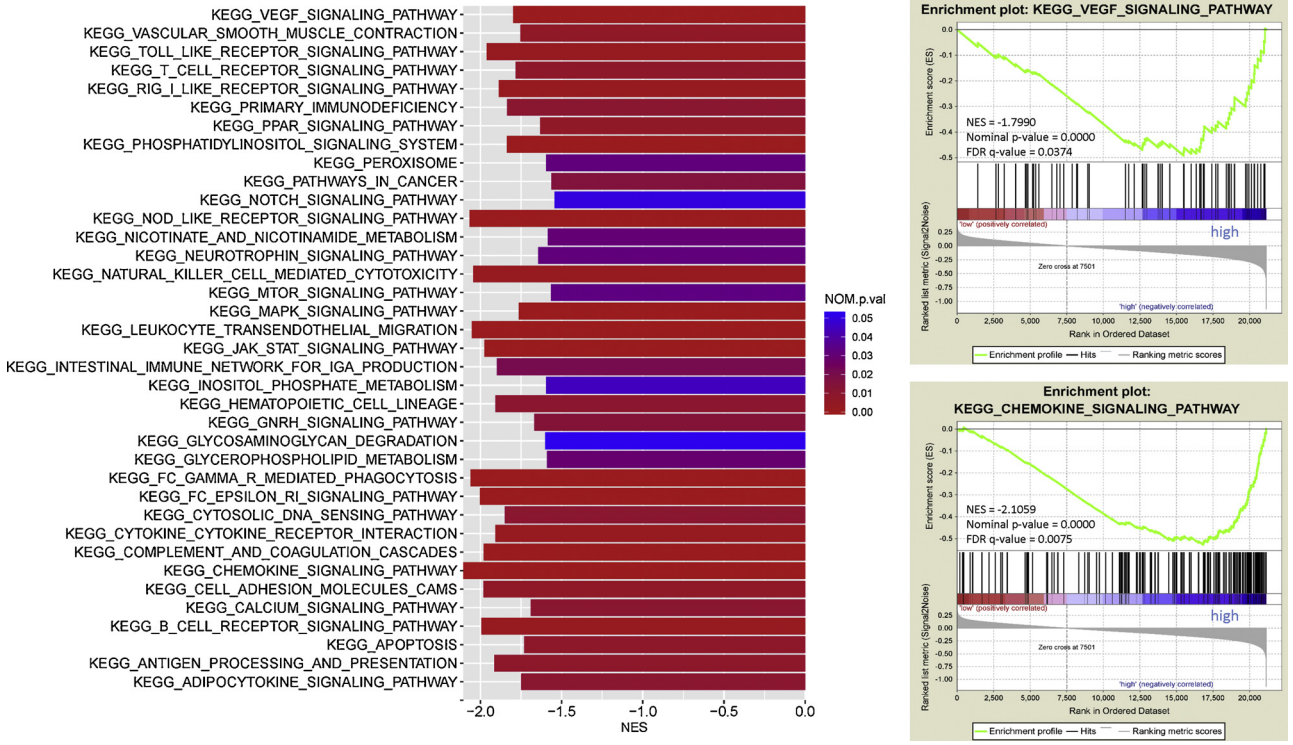

Fig. 3. Enrichment plots from KEGG for significant enrichment functions (normal p-value < 0.05 and FDR < 0.25). NES: normalized enrichment score; FDR: false discovery rate.

apoptosis, metabolism, complement, vascular endothelial growth factor (VEGF) signaling, chemokine signaling, and B-cell receptor signaling were also differentially enriched in STAT5A high expression phenotype (Fig. 3).

4. Discussion

Recently, the expression and functions of STAT5A have been reported in some types of human cancers [4,25,36,38]. STAT5A mediated the role of cytokines, growth factors and hormones on gene expression [26]. STAT5A is activated by growth hormone in UMR 106 osteosarcoma cell line [16]. STAT5A was originally identified as a "mammary gland factor" which was found to induce transcription of milk protein genes [5]. STAT5A impact breast cancer cell differentiation, proliferation, and survival and plays an important role in the initiation and progression of breast cancer [12]. STAT5A has been identified as an important factor for prostate cancer cell viability and tumor growth and contributes to metastatic dissemination of prostate cancer [8]. To our knowledge, the expression of STAT5A and its potential prognostic impact on patients with osteosarcoma has not yet been identified, the potential role of STAT5A in osteosarcoma was focused on the present study.

In the present study, we found that low expression of STAT5A was closely correlated with progression of osteosarcoma patients. Moreover, low expression of STAT5A was significantly associated with poor EFS and OS and short survival time of patients by multivariate analyses. To further investigate the functions of STAT5A in osteosarcoma, GSEA was performed. Our study suggested that complement, metabolism, apoptosis, interferon-gamma response, inflammatory response, and Notch, Kras, reactive oxygen species, p53, VEGF signaling pathways, as well as immune-related signaling pathways such as IL-6/JAK/STAT3, IL-2/Stat5, chemokine, and B-cell receptor etc. were significantly enriched in STAT5A high expression phenotype. This suggested that STAT5A may serve as a potential prognostic marker to identify patients with poor clinical outcome and may act as a potential therapeutic target in osteosarcoma.

Researches reveal that STAT5A may promote malignant transformation and enhance tumor growth in breast cancer and prostate carcinoma [30,31]. Decreased STAT5A expression showed a positive correlation with poor prognosis in some human cancers, including breast cancer [36], ovarian cancer [10], and follicular lymphoma [32]. Reduced expression of STAT5A was associated with more advanced histological differentiation of breast cancer [36]. In the present study, our work was the first to demonstrate that low expression of STAT5A was associated with the progression of osteosarcoma and predicted poor prognosis of osteosarcoma patients.

The genetic alterations of p53 are frequent in human osteosarcoma cells. Mutations in p53 have been identified to play an important role in cell proliferation and in the pathogenesis of osteosarcoma [14,15]. STAT5A is identified as a p53-target gene [19]. STAT5A is a crucial regulator of the immune system. STAT5A enhances to B-cell responses to chemokines and induces the growth of lymphoma/leukemia cells [34]. VEGF plays a crucial role in diverse cellular functions such as cellular adhesion, proliferation, migration, and invasion [20]. VEGF level is significantly correlated with prognosis in several common cancers including osteosarcoma [40]. STAT3 may involve in the signal transduction pathways activated by VEGF in human hemopoietic progenitor cells [37]. In this study, we observed that the complemen, metabolism, apoptosis, interferon-gamma response, inflammatory response, Notch, Kras, reactive oxygen species, VEGF, IL-6/JAK/STAT3, IL-2/Stat5, B-cell receptor, and p53 pathways were significantly associated with high expression of STAT5A, which were the first to be reported in osteosarcoma, and the regulatory mechanism of STAT5A needs to be further elucidated.

In conclusion, the current study revealed that STAT5A may serve as both a clinically relevant indicator of disease progression and may be a potential prognostic molecular marker of poor prognosis in patients with osteosarcoma. Moreover, the complement, metabolism, apoptosis, interferon-gamma response, inflammatory response, and Notch, Kras, reactive oxygen species, p53, VEGF signaling pathways, as well as immune-related signaling pathways such as IL-6/JAK/STAT3, IL-2/Stat5, chemokine, and B-cell receptor etc. may be the key biological functions and potential molecular pathways regulated by STAT5A in osteosarcoma. Further study should be performed to validate the biologic role of STAT5A in osteosarcoma.

Author contributors

Zonghui Guo and Yin Tang contributed to the conception and design of this research. Zonghui Guo, Yin Tang, Youwei Fu, and Junjie Wang contributed to the drafting of the article and final approval of the submitted version. Zonghui Guo, Yin Tang, Youwei Fu, and Junjie Wang contributed to data analyses and the interpretation and completion of the figures and tables. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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