Expression Status and Prognostic Values of SOCS Family Genes in Non-small Cell Lung Cancer

Xuede Zhang (zxd1978cn@163.com)
Beilun District People's Hospital

Kai Sun
Liuzhou People's Hospital

Lingling Bao
Beilun District People's Hospital

Research Article

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Abstract

Background: Suppressors of cytokine signaling (SOCS) family play important roles in the development of cancers by inhibiting the transmission of the Janus kinases–signal transducers and activators of transcription (JAK-STAT) signaling pathway. However, the expression patterns and prognostic value of SOCS family genes in non-small cell lung cancer (NSCLC) remains unclear.

Methods: The SOCS family genes expression profiles were explored using ONCOMINE and GEPIA online tools. The mutation and copy number alterations of SOCS family genes in NSCLC were assessed by cBioportal for Cancer Genomics. The methylation status of SOCS family members were analyzed through MEXPRESS and UCSC Xena website. The prognostic values of SOCS family genes in NSCLC were explored through Kaplan-Meier Plotter database.

Results: The expression levels of SOCS2, SOCS3, and cytokine-inducible SH2-containing protein (CISH) were significantly reduced in NSCLC tissues compared to normal lung tissues. The aberrant DNA methylation of SOCS family genes were frequent in NSCLC. CISH methylation was negatively correlated with gene expression in NSCLC. The Kaplan-Meier Plotter analysis demonstrated high expression of SOCS1 may be a predictor of poor prognosis in lung adenocarcinoma (LUAD) but served as a favorable prognostic marker of lung squamous cell carcinoma. The high expression levels of SOCS2 and SOCS4-7 were significantly correlated with better overall survival (OS) in LUAD but not in lung squamous carcinoma (LUSC) patients.

Conclusions: Our findings indicated that the aberrant gene expression and DNA methylation of SOCS family members are common in NSCLC and contribute to tumorigenesis. SOCS family genes may serve as therapeutic targets and prognostic biomarkers for NSCLC patients.

Introduction

Lung cancer is one of the most common malignant tumors with the highest incidence and mortality worldwide[1]. Non-small cell lung cancer (NSCLC) accounts for 80%-85% of all lung cancers[2]. Although in recent years, the treatment of NSCLC has made significant progress, such as targeted therapy and immunotherapy, the five-year survival rate of patients with advanced NSCLC is still less than 16%[3]. Therefore, it is very essential to identify novel targets and prognostic biomarkers for the treatment of NSCLC cancer.

It is well known that Janus kinase (JAK)-signal transducer and activators of transcription (STAT) signaling pathways play essential roles in various human malignancies, which are involved in diverse pathophysiological processes, including proliferation, apoptosis, immune responses, and stem cell differentiation[4]. SOCS play pivotal roles in the development of cancers by negatively regulating the JAK-STAT pathway. This family of SOCS contains eight members, SOCS1–7 and cytokine-inducible SH2-containing protein (CISH), which are characterized by the presence of similar structural domains that include a central SH2 (Src Homology 2) domain, a C-terminal SOCS box region, and an N-terminal region...
of variable length. [5–7]. Previous studies demonstrated that SOCS family members were abnormally expressed in various cancers and may serve as prognostic biomarkers. Besides, many studies have shown that SCOS expression was dysregulated in various cancers and played an important role in tumor development and progression[8–10]. Previous research suggests that SOCS family genes can be regarded as prognostic markers of breast cancer and gastric cancer patients [11–13].

DNA mutations and abnormal methylation have been considered important factors of tumorigenesis. There is evidence showing that lymphoma patients have a higher SOCS1 mutation rate[14, 15]. In addition, a high mutation rate in SOCS genes was observed in patients with ovarian cancer[16]. SOCS genes methylation may play important roles in carcinogenesis and tumor progression and may be used as diagnostic and prognostic tumor biomarkers[17–20].

The expression status and prognostic values of SOCS family genes in NSCLC are limited and the results remain unclear[21–23]. In the present study, we first comprehensively explored the expression patterns and prognostic values of eight SOCS family genes in NSCLC using bioinformatics methods.

**Materials And Methods**

**ONCOMINE analysis**

The ONCOMINE is a cancer microarray database and integrated data-mining platform, which allows researchers to facilitate analysis of interest from public gene expression database[24]. We compared the mRNA expression levels of SOCS family genes between various cancer tissues and corresponding normal tissues through ONCOMINE online tool. The thresholds were as follows: P-value was defined as 1E-4, fold change = 2, gene rank was TOP 10% and data type was mRNA.

**GEPIA (Gene Expression Profiling Interactive Analysis)**

GEPIA is an interactive online tool for analyzing gene expression data based on TCGA and the GTEx dataset[25]. We explored SOCS family genes expression profiles in lung cancer tissues and corresponding normal tissues using the GEPIA website. The thresholds were as follows:|Log2FC| Cutoff = 1, \( P \)-value ≪ 0.05.

**cBioPortal for Cancer Genomics**

The cBioPortal for Cancer Genomics is an open-source bioinformatics platform, which provides rapid, intuitive, and high-quality access to visualize and analyze complex genomic data and clinical profiles[26]. We assessed the mutation and copy number alterations of SOCS family genes in NSCLC through the cBioportal for Cancer Genomics.

**UCSC Xena analysis**

UCSC Xena is a visual exploration resource for both public and private omics data, which allows researchers to explore relationships among genomic including DNA methylation and clinical data based
results on large public cancer genomics datasets[27]. In this study, we explored methylation levels of SOCS family genes between normal lung tissues and tumor tissues, correlations between gene methylation and expression levels, and survival analysis based on methylation levels in NSCLC using UCSC Xena online exploration tool. Regarding the prognostic value of 8 SOCS genes methylation, NSCLC patients were divided into ‘low’ and ‘high’ expression groups based on the individual SOCS family genes methylation levels used the median value as the cutoff point. $P$-value of $<0.05$ indicated statistical significance.

**MEXPRESS analysis**

MEXPRESS is an intuitive web tool, which facilitated integration and visualization of gene expression, DNA methylation, and clinical data based on the TCGA dataset[28]. The methylation status of SOCS family members were analyzed through MEXPRESS website.

**Kaplan-Meier plotter analysis**

The Kaplan-Meier plotter is an online survival analysis website, which was used to assess the prognostic value of SOCS family genes expression in NSCLC based GEO, EGA, and TCGA datasets. Additionally, we analyzed the association between SOCS family genes expression and OS based on various clinicopathological features including histology and stage. Patients with NSCLC were divided into high and low expressing groups based on the median value of individual SOCS family genes mRNA expression. $P<0.05$ was considered significant.

**Results**

**Expression patterns of SOCS family genes in NSCLC patients**

Expression levels of 8 SOCS family genes in cancers were compared with those in normal samples using ONCOMINE databases (Fig. 1). The results showed mRNA expression levels of SOCS2, SOCS3 and CISH were significantly reduced in patients with lung cancer compared to normal lung tissues. Analysis of 6 datasets showed that SOCS2 mRNA expression levels were significantly decreased in lung adenocarcinoma (LUAD) compared with that in normal lung tissues[29–34] (Table 1). In Hou’s dataset[32], low expression levels of SOCS2 were also found in large cell lung carcinoma and lung squamous cell carcinoma (LUSC) compared to in normal lung tissues (Fold changes were −7.159 and, -3.074 respectively). Hou’s dataset also indicated SOCS3 were significantly down-regulated in large cell lung carcinoma, LUSC, and LUAD[32]. In addition, low expression of SOCS3 was also found in LUAD compared to that in normal lung tissues by Selamat[30]. We also found that CISH expression was downregulated in large cell lung carcinoma and LUSC compared with normal lung tissues in In Hou’s dataset[32]. However, no significant difference was observed in SOCS1, SOCS4-7 between lung cancer and normal tissues. We also assessed the mRNA expression of 8 SOCS family genes between NSCLC and normal lung tissues Using GEPIA online tool. Our findings showed the expression of SOCS2 and SOCS3 were decreased in LUAD and LUSC compared to those in normal lung tissues. CISH was only
downregulated in LUSC (Fig. 2). We further analyzed the relationship between the expression levels of SOCS family genes and tumor stage of NSCLC patients. The results indicated that there were significant differences in SOCS1 and CISH expression between the various NSCLC stages, but not in other SOCS family genes (Fig. 3).

**Genetic mutation and copy number alterations of SOCS family genes in NSCLC**

We analyzed the genetic alterations of SOCS genes in NSCLC through integrating 6 databases from the cBioPortal for Cancer Genomics. Oncoprint representation from cBioPortal revealed the distribution of SOCS genes alterations in NSCLC (Fig. 4). The genetic alterations frequencies of SOCS members were low (0.6% ~ 3%) included missense mutation, truncating mutation, fusion, amplification, and deep deletion. Among them, amplification occurred most frequently.

**Methylation analysis of SOCS family genes in NSCLC**

The DNA methylation levels of SOCS family genes between normal lung tissues and NSCLC tissues were analyzed through UCSC Xena. The results showed DNA methylation levels of SOCS1, SOCS3-5, and CISH are significantly decreased in LUAD compared with normal lung tissues (Fig. 5A.). However, DNA methylation levels of SOCS2 and SOCS7 are significantly increased in LUAD tissues compared with normal lung tissues (Fig. 5A.). There was no significant difference between the methylation levels of SOCS6 in the lung normal and adenocarcinoma tissues. In LUSC patients, DNA methylation levels of SOCS1,3, and SOCS5,6 are significantly decreased in tumor tissues compared with normal tissues (Fig. 5B.). DNA methylation levels of SOCS7 and CISH are significantly increased in tumor tissues compared with normal lung tissues (Fig. 5B.). However, no significant difference between the methylation levels of SOCS2 and SOCS4 were observed in the lung normal and LUSC tissues. The levels of DNA methylation at multiple sites of SOCS family genes also were analyzed through MEXPRESS website. As presented in Supplementary Fig. 1, for the majority of SOCS family members, DNA methylation levels at multiple sites are significantly decreased in NSCLC compared with normal lung tissues. The same result was also observed in LUSC patients. (Supplementary Fig. 2)

Next, we further explored the correlation between DNA methylation and gene expression levels of SOCS family members in NSCLC patients. Our findings suggested there was a modest negative correlation between DNA methylation density and gene expression levels of CISH in both LUAD (Pearson's correlation, \( r = -0.5654, P<0.01 \)) and LUSC (Pearson's correlation, \( r = -0.4544, P<0.01 \)). (Fig. 6). Finally, we analyzed the relationship between DNA methylation beta values of 8 SOCS family genes and prognosis in NSCLC patients. The results showed LUAD patients with CISH hypermethylation exhibited longer OS (\( P<0.01 \)) than those with CISH hypomethylation (Fig. 7). However, there is no correlation between other SOCS genes methylation levels and prognosis in NSCLC patients.
Prognostic values of SOCS family genes in NSCLC patients

The prognostic values of SOCS family genes in NSCLC patients were performed using the Kaplan-Meier Plotter website. In LUAD subgroups, Kaplan-Meier survival curves showed low mRNA expression of SOCS1 was significantly associated with better OS. (Fig. 8 HR = 1.37, 95% CI: 1.08–1.73, log-rank \( P = 0.0084 \)). However, the high expression levels of SOCS2 and SOCS4-7 was significantly correlated with better OS (Fig. 8). The mRNA expression levels of SOCS3 and CISH were not correlated with OS. In LUSC subgroups, Kaplan-Meier survival curves showed patients with high SOCS1 expression had longer OS than patients with low SOCS1 expression. (Fig. 9 HR = 0.77, 95% CI: 0.61–0.97, log-rank \( P = 0.027 \)). The mRNA expression levels of the other SOCS family members were not correlated with OS (Fig. 9).

Subsequently, we further investigated the relationship between SOCS family genes in NSCLC patients with different clinical stages. As shown in Table 2, SOCS1 high expression was correlated with shorter OS in LUAD patients with stage I (HR = 2, 95%CI: 1.34–2.98, logrank \( P = 0.00052 \)). Similarly, SOCS3 high expression was correlated with shorter OS in LUAD patients with stage II. In contrast, the high mRNA expression levels of SOCS2, SOCS5- SOCS7 were significantly related to better OS in LUAD with stage I/II. For all LUAD stages (I-III), SCOS4 high expression indicated better OS. From Table 3, SOCS1 high expression was correlated with longer OS in LUSC patients with stage I (HR = 0.52, 95%CI: 0.34–0.81, logrank \( P = 0.0028 \)). The high expression levels of SOCS2 and SOCS7 were correlated with better OS in LUSC patients with stage II. In contrast, SOCS6 high expression was weakly associated with worse OS in LUSC patients with stage II (HR = 2.77, 95%CI: 0.96–8.01, logrank \( P = 0.049 \)).
Table 1
Correlation of SOCS expression with OS in different stages of LUSC patients.

| lung cancer vs. normal                                      | Fold change | P value     | Ref       |
|-------------------------------------------------------------|-------------|-------------|-----------|
| SOCS1                                                       | NS          |             |           |
| SOCS2                                                       |             |             |           |
| Lung Adenocarcinoma vs. Normal                              | -4.843      | 1.67E-12    | Su Lung   |
| Lung Adenocarcinoma vs. Normal                              | -2.924      | 5.68E-25    | Selamat Lung |
| Lung Adenocarcinoma vs. Normal                              | -2.561      | 1.58E-16    | Landi Lung |
| Lung Adenocarcinoma vs. Normal                              | -3.854      | 2.32E-14    | Hou Lung   |
| Large Cell Lung Carcinoma vs. Normal                        | -7.159      | 7.69E-8     | Hou Lung   |
| Squamous Cell Lung Carcinoma vs. Normal                     | -3.074      | 3.51E-11    |           |
| Lung Adenocarcinoma vs. Normal                              | -2.450      | 6.44E-5     | Stearman Lung |
| Lung Adenocarcinoma vs. Normal                              | -2.861      | 3.17E-9     | Okayama Lung |
| SOCS3                                                       |             |             |           |
| Large Cell Lung Carcinoma vs. Normal                        | -3.985      | 3.50E-11    | Hou Lung   |
| Squamous Cell Lung Carcinoma vs. Normal                     | -3.038      | 6.32E-14    |           |
| Lung Adenocarcinoma vs. Normal                              | -2.565      | 2.14E-11    |           |
| Lung Adenocarcinoma vs. Normal                              | -2.698      | 2.75E-14    | Selamat Lung |
| SOCS 4–7                                                    | NS          |             |           |
| CISH                                                        |             |             |           |
| Large Cell Lung Carcinoma vs. Normal                        | -2.666      | 4.64E-12    | Hou Lung   |
| Squamous Cell Lung Carcinoma vs. Normal                     | -2.014      | 6.45E-15    |           |

NS, no statistical differences.
Table 2
Correlation of SOCS expression with OS in different stage of LUAD patients.

| Gene  | Stage | Cases | HR (95% CI)       | p-value |
|-------|-------|-------|-------------------|---------|
| SOCS1 | I     | 370   | 2 (1.34–2.98)     | 0.00052 |
|       | II    | 136   | 1.22 (0.75–1.97)  | 0.43    |
|       | III   | 24    | 1.18 (0.41–3.37)  | 0.76    |
| SCOS2 | I     | 346   | 0.3 (0.19–0.48)   | 1.2e-07 |
|       | II    | 118   | 0.53 (0.31–0.92)  | 0.021   |
|       | III   | 21    | 0.37 (0.11–1.2)   | 0.083   |
| SCOS3 | I     | 346   | 1.15 (0.77–1.72)  | 0.48    |
|       | II    | 118   | 2 (1.14–3.48)     | 0.013   |
|       | III   | 21    | 0.79 (0.26–2.38)  | 0.67    |
| SOCS4 | I     | 370   | 0.27 (0.17–0.44)  | 8.8e-09 |
|       | II    | 118   | 0.48 (0.28–0.84)  | 0.009   |
|       | III   | 21    | 3.35 (1.02–11.01) | 0.036   |
| SCOS5 | I     | 370   | 0.3 (0.19–0.46)   | 1.3e-08 |
|       | II    | 136   | 0.43 (0.26–0.7)   | 0.00052 |
|       | III   | 24    | 0.42 (0.14–1.2)   | 0.094   |
| SCOS6 | I     | 346   | 0.41 (0.27–0.63)  | 3e-05   |
|       | II    | 118   | 0.66 (0.39–1.13)  | 0.13    |
|       | III   | 21    | 1.57 (0.46–5.41)  | 0.47    |
| SOCS7 | I     | 346   | 0.38 (0.25–0.59)  | 8.9e-06 |
|       | II    | 118   | 0.53 (0.31–0.91)  | 0.019   |
|       | III   | 21    | 0.49 (0.15–1.65)  | 0.24    |
| CISH  | I     | 346   | 0.92 (0.62–1.37)  | 0.68    |
|       | II    | 118   | 1.56 (0.92–2.65)  | 0.096   |
|       | III   | 21    | 0.69 (0.23–2.06)  | 0.51    |
### Table 3
Correlation of SOCS expression with OS in different stage of LUSC patients.

| Gene   | Stage | Cases | HR (95% CI)         | p-value |
|--------|-------|-------|---------------------|---------|
| SOCS1  | I     | 172   | 0.52 (0.34 - 0.81)  | **0.0028** |
|        | II    | 100   | 0.71 (0.39 - 1.29)  | 0.26    |
|        | III   | 43    | 1.12 (0.57 - 2.24)  | 0.74    |
| SCOS2  | I     | 74    | 0.95 (0.52 - 1.73)  | 0.88    |
|        | II    | 39    | 0.31 (0.1 - 0.97)   | **0.033** |
|        | III   | 20    | 1.24 (0.46 - 3.35)  | 0.68    |
| SCOS3  | I     | 74    | 0.72 (0.4 - 1.31)   | 0.28    |
|        | II    | 39    | 0.77 (0.29 - 2.05)  | 0.6     |
|        | III   | 20    | 1.96 (0.69 - 5.57)  | 0.2     |
| SOCS4  | I     | 74    | 1.18 (0.65 - 2.14)  | 0.59    |
|        | II    | 39    | 1.91 (0.69 - 5.27)  | 0.2     |
|        | III   | 20    | 1.12 (0.43 - 2.92)  | 0.82    |
| SCOS5  | I     | 172   | 0.82 (0.53 - 1.25)  | 0.35    |
|        | II    | 100   | 1.91 (0.69 - 5.27)  | 0.2     |
|        | III   | 43    | 1.44 (0.73 - 2.84)  | 0.3     |
| SCOS6  | I     | 74    | 1.38 (0.76 - 2.53)  | 0.29    |
|        | II    | 39    | 2.77 (0.96 - 8.01)  | **0.049** |
|        | III   | 20    | 1.89 (0.7 - 5.11)   | 0.2     |
| SOCS7  | I     | 74    | 1.45 (0.79 - 2.68)  | 0.23    |
|        | II    | 39    | 0.33 (0.11 - 0.95)  | **0.031** |
|        | III   | 20    | 0.46 (0.17 - 1.25)  | 0.12    |
| CISH   | I     | 74    | 0.68 (0.37 - 1.24)  | 0.21    |
|        | II    | 39    | 0.52 (0.19 - 1.44)  | 0.2     |
|        | III   | 20    | 1.33 (0.48 - 3.71)  | 0.58    |

**Discussion**
In the present study, we comprehensively explored the expression profiles and DNA methylation status of SOCS family members in NSCLC and further analyzed their prognostic values in NSCLC patients through online bioinformatics tools. Our findings suggest that the expression levels of SOCS2 and SOCS3 were lower in NSCLC tissues compared to those in normal lung tissues. CISH was also downregulated in LUSC. The survival analysis results showed SOCS1 expression was a favorable prognostic factor in LUSC but was a worse prognostic factor in LUAD. SOCS2 and SOCS4-7 were potential prognostic factors in LUAD but not in LUSC patients. The results of methylation analysis indicated SOCS family genes showed aberrant DNA methylation in NSCLC tissues compared with normal lung tissues. The result also suggested CISH gene expression levels were inversely related to DNA methylation levels in NSCLC and CISH hypermethylation were associated with longer OS in LUAD patients.

SOCS1 may play an important role in regulating tumor growth and proliferation by exerting two major functions: Firstly, it can inhibit the transmission of the JAK-STAT signaling pathway as a negative regulatory protein [22, 35]. Secondly, it may be involved in ubiquitination and subsequent proteasomal degradation as a substrate-recognition module via the recruitment of E3 ubiquitin ligases complex [36, 37]. Previous studies demonstrated that SOCS1 was low expression in many types of cancer, such as anaplastic thyroid cancer [38], gastric cancer [39], hypopharyngeal carcinoma [40], and breast cancer [41]. However, several studies have also shown that SOCS1 expression level was increased in colorectal cancer [42], glioblastoma [43], and triple-negative breast cancer [44]. Several studies indicated SOCS-1 was downregulated in lung cancer and exerted an antitumor effect by suppressing the JAK/STAT [21, 45]. However, we found no obvious differences in SOCS1 expression between NSCLC tissues and normal lung tissues by integrating the public database. The reason for inconsistent was unclear, possibly due to the limited sample size in the previous study. The results also indicated that SOCS1 was downregulated in advanced-stage lung cancer. Li et al also found the expression of SOCS1 was decreased in metastatic sites of malignant melanoma [46]. These findings suggested the deletion of SOCS1 may promote the tumor progression of NSCLC.

As studies showed, SOCS1 promoter was frequently aberrantly methylated in tumor tissues [47, 48]. Several studies showed methylation rates of SOCS1 in hepatocellular carcinoma tissues were significantly higher than those in normal liver tissues [17, 49]. It was also reported that SOCS1 methylation levels were increased in colorectal cancer samples compared to controls and methylation of SOCS-1 was associated with suppression of SOCS-1 expression in tumors [19].

In addition, a study revealed that methylation of SOCS1 was in lung cancer tissues higher (2.72-fold) than that in adjacent non-malignant tissue [50]. In contrast, our findings showed DNA methylation levels of SOCS1 are significantly decreased in both LUAD and LUSC compared with normal lung tissues by UCSC Xena online tool. The similar results were verified by MEXPRESS analysis. However, no significant correlation was observed between SOCS1 promoter methylation and gene expression in this study.

It was reported that high expression of SOCS1 predicted favorable prognosis for hepatocellular carcinoma patients [51]. The similar results were observed in breast cancer [11], gastric cancer [13], and
head and neck squamous cell carcinoma [52]. Consistent with previous studies, our findings also indicated high expression of SOCS1 was correlated with better OS in LUSC patients. Surprisingly, contrary conclusions were drawn in LUAD subgroups and low mRNA expression of SOCS1 was significantly associated with better OS. The reason is not clear. We speculate that the reason might be due to the posttranscriptional regulation of the SOCS1 mRNA in different histological types of lung cancer.

Recent studies have reported that SOCS2 expression was downregulated in various cancers including breast cancer [41], hepatocellular carcinoma [53], and colorectal cancer [54]. Our findings are consistent with the previously mentioned studies. We also found SOCS2 expression was decreased in LUAD and LUSC through ONCOMINE and GEPIA analysis. Our findings indicated the high expression level of SOCS2 predicted better OS in LUAD patients but not in LUSC patients. Several studies suggested high SOCS2 expression may be served as an independent predictor of good prognosis in breast cancer [55], prostate cancer [56], and hepatocellular carcinoma [57]. In this study, increased levels of SOCS2 methylation have also been observed in LUAD patients. Consistent with our findings, SOCS2 was also found to be hypermethylated in human melanoma [58] and ovarian cancers [59].

It was reported that SOCS3 expression was downregulated in various cancers including lung cancer tissues and cells [60], hepatocellular carcinoma [61], and gastric cancer [62]. In this study, our findings also confirm the above view. Several studies showed SOCS3 promoter methylation resulted in decreased gene expression [63, 64]. A small number of studies suggested frequent hypermethylation of SOCS3 promoter was correlated with gene silencing in NSCLC cell lines and tumor tissues [65, 66]. However, several studies also indicated no methylation on SOCS3 in NSCLC [67, 68]. In the present study, SOCS3 hypomethylation was observed in NSCLC. Previous studies indicated high expression of SOCS3 may be a better prognostic marker in hepatocellular carcinoma [69], gastric cancer [70], and colorectal cancer [71]. To our knowledge, the relationship between SOCS3 and prognosis of patients with NSCLC has not been reported. In this study, no correlation between SOCS3 expression and prognosis of lung cancer patients was found.

SOCS4-7 genes were found to have identical long N-terminal domain and those genes may have similar expression patterns in tumor and normal tissues. To date, the studies regarding the relationship between SOCS4-7 and cancer are relatively rare. We found no differences in SOCS4-7 gene expression between lung cancer and normal tissues in this study. Kobayashi et al reported that gastric cancer tissues exhibited promoter hypermethylation of the SOCS4 gene and gene expression was significantly decreased in gastric cancer tissues compared to normal tissues [72]. The study from Sasi et al indicated SOCS4-7 expression decreased with increased TNM stage and high expression levels of SOCS 4 and SOCS7 were associated with better OS in breast cancer [12]. Yoon et al explored expression patterns of SOCS5 and SOCS6 in a variety of normal and tumor tissues and found these two genes had similar expression patterns in most tumors and healthy tissues [73]. The results showed SOCS5 and SOCS6 were downregulated in normal tissues included ovary, stomach, lung, bladder, and prostate, whereas the expression levels of these two genes were high in uterus, thyroid grand, and pancreas tissues. The study
also suggested the expression levels of SOCS5 and SOCS6 were increased in ovary, stomach, and lung cancer tissues, and decreased in thyroid gland cancer.

Our findings indicated the high expression levels of SOCS4-7 was significantly correlated with better OS for LUAD patients. It was also demonstrated that hepatocellular carcinoma patients with high expression of SOCS6 had significantly longer OS[57].

CIS encoded by the gene CISH is the first identified SOCS family member, but there are not many studies on CISH in tumors. It was reported CISH gene expression was increased in human breast cancer and promoted cell proliferation and colony formation [74]. In our study, CISH was only downregulated in LUSC patients but not in LUAD. To date, the association between CISH expression and prognosis has not been reported. In our study, we did not also find relationship between CISH expression and prognosis in lung cancer. Our findings indicated methylation levels of CISH was higher in LUSC but lower in LUAD compared with that in normal lung tissues. We observed that DNA methylation of CISH was negatively correlated with gene expression in NSCLC. It was demonstrated hypermethylation of CISH is infrequent in Philadelphia-negative myeloproliferative neoplasm [75] and hepatocellular carcinoma [76]. These results were inconsistent due to the small sample size. Therefore, further research is required to investigate the role of CISH in cancer development.

Conclusion

In the present study, we comprehensively evaluated gene expression profiles, DNA methylation profiles, and prognostic value of SOCS family genes in NSCLC. Our findings suggested SOCS2, SOCS3, and CISH were downregulated in NSCLC and may serve suppressive roles in tumor development. Furthermore, aberrant DNA methylation of SOCS genes were frequent in NSCLC and likely lead to tumorigenesis. Finally, the high expression of most SOCS family members predicted better OS in NSCLC patients, but high mRNA expression of SOCS1 may be a predictor of poor prognosis in LUAD. Although the underlying mechanism of SOCS genes in the development of NSCLC was not entirely clear, our findings indicated that SOCS genes may serve as prognostic biomarkers and promising therapeutic targets for NSCLC.

Abbreviations

SOCS: Suppressors of cytokine signaling; JAK-STAT: Janus kinases signal transducers and activators of transcription; NSCLC: non-small cell lung cancer; CIS/CISH: cytokine-inducible SH2-containing protein; LUAD: lung adenocarcinoma; OS: overall survival; LUSC: lung squamous carcinoma.

Declarations

Conflicts of interest

The authors declare that they have no competing interests.
Author contributions

XZ wrote the manuscript. KS and LB provided the design idea of this study. XZ and LB processed the data and supplemented the ideas. All authors reviewed the manuscript.

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Ethics approval and consent to participate

The data of this article were derived from the published literature and the online websites, ethical approval is not required.

Consent for publication

Not applicable

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Not applicable

Availability of data and materials

The mRNA expression levels of SOCS family genes between various cancer tissues and corresponding normal tissues were analyzed through ONCOMINE (www.oncomine.org). GEPIA (http://gepia.cancer-pku.cn/detail.php) is used to analyze the RNA sequencing expression data of SOCS family genes from TCGA and GTEx projects via standard processing pipelines. The mutation and copy number alterations of SOCS family genes in NSCLC through the cBioportal for Cancer Genomics. (www.cbioportal.org), and datasets analysed during the section are included in this Figure4. The methylation levels of SOCS family genes between normal lung tissues and tumor tissues, correlations between gene methylation and expression levels, and survival analysis based on methylation levels in NSCLC using UCSC Xena online. (https://xenabrowser.net/). The datasets analyzed in the section were based on TCGA lung adenocarcinoma and lung squamous cell carcinoma. The levels of DNA methylation at multiple sites of SOCS family genes also were analyzed based on the TCGA dataset through MEXPRESS website (https://mexpress.be/). Kaplan-Meier plotter (http://kmplot.com/analysis/) is used to determine the prognostic values of SOCS family genes in NSCLC.

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Figures
### Figure 1

Expression status of SOCS in NSCLC from ONCOMINE

| Analysis Type by Cancer | SOCS1 | SOCS2 | SOCS3 | SOCS4 | SOCS5 | SOCS6 | SOCS7 | CISH |
|------------------------|-------|-------|-------|-------|-------|-------|-------|------|
| Bladder Cancer         | 2     | 4     | 2     | 2     | 1     | 2     | 2     | 1    |
| Brain and CNS Cancer   | 2     | 7     | 1     | 8     | 1     | 1     | 2     | 2    |
| Breast Cancer          | 1     | 3     | 1     | 10    | 1     | 1     | 1     | 1    |
| Cervical Cancer        | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Colorectal Cancer      | 2     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Esophageal Cancer      | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Gastric Cancer         | 2     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Head and Neck Cancer   | 1     | 2     | 2     | 1     | 1     | 1     | 1     | 1    |
| Kidney Cancer          | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Leukemia               | 3     | 7     | 1     | 2     | 1     | 1     | 2     | 1    |
| Liver Cancer           | 2     | 8     | 4     | 3     | 1     | 1     | 2     | 1    |
| Lung Cancer            | 7     | 3     | 1     | 2     | 1     | 1     | 1     | 2    |
| Lymphoma               | 2     | 2     | 4     | 2     | 1     | 1     | 1     | 1    |
| Melanoma               | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Myeloma                | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Other Cancer           | 2     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Ovarian Cancer         | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Pancreatic Cancer      | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Prostate Cancer        | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |
| Sarcoma                | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1    |

- **Significant Unique Analyses**: 13, 5, 22, 41, 13, 27, 8, 1, 4, 3, 1, 10, 5, 8
- **Total Unique Analyses**: 333, 346, 334, 204, 345, 319, 318, 300

Legend:
- 1
- 5
- 10
- 5
- 1

%
Figure 2

Expression profiles of SOCS in NSCLC from GEPIA A. SOCS genes expression profiles. B. SOCS genes expression on Box Plots
Figure 3

Relationship between expression levels of SOCS and stage of NSCLC patients.

Figure 4

Genetic alteration of SOCS in NSCLC from the cBioPortal for Cancer Genomics.
Figure 5

DNA methylation status of SOCS in NSCLC from UCSC. A. DNA methylation status of SOCS in LUAD. B. DNA methylation status of SOCS in LUSC.
Figure 6

Prognostic values of SOCS in LUAD using the Kaplan-Meier Plotter database.
Figure 7

Prognostic values of SOCS in LUSC using the Kaplan-Meier Plotter database.

Figure 8

Correlation between DNA methylation and gene expression levels of CISH in NSCLC patient A. Correlation between DNA methylation and gene expression of CISH in LUAD. B. Correlation between DNA methylation
and gene expression of CISH in LUSC

Figure 9

Relationship of CISH methylation and Prognosis in NSCLC. A. Relationship of CISH methylation and Prognosis in LUAD. B. Relationship of CISH methylation and Prognosis in LUSC.

Supplementary Files

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