Original Research

Mining database for the expression and clinical significance of STAT family in head and neck squamous cell carcinomas

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A R T I C L E  I N F O

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A B S T R A C T

Background: Head and neck squamous cell carcinomas (HNSC) are among the most common malignant tumors with high incidence, relapse, and mortality rate. STAT proteins are implicated in various biological processes, including cell proliferation, metastasis, and immune regulation.

Method: Various bioinformatics tools were used to explore the role of the STAT family in HNSC.

Result: The mRNA levels of STAT1/2/4/5A/6 were significantly upregulated in HNSC tissues. The levels of STAT1/2/4/5A/6 could be used for the detection of HNSC. HNSC patients with a high level of STAT5A had a poor overall survival and relapse-free survival. A moderate to high correlation was obtained between the STAT family and HNSC. Genetic alteration revealed that STAT1/2/3/4/5A/5B/6 were altered in 6%, 5%, 7%, 8%, 6%, 6%, and 4% of the queried TCGA HNSC samples, respectively. Immune infiltrations analysis suggested a significant association between STAT5A expression and abundance of specific immune cells. Further, copy number alteration of STAT5A could certainly inhibit infiltration level. Moreover, a close correlation was obtained between STAT5A level and the expression of immune markers in HNSC. Several kinase targets and transcription factor targets of STAT5A in HNSC were also identified. Enrichment analysis suggested that STAT5A and co-expression genes were mainly responsible for adaptive immune response, T cell activation, cytokine-cytokine receptor interaction, chemokine signaling pathway, cell-adhesion molecules, and ribosome and RNA transport.

Conclusion: Our results provided additional data for the expression and clinical significance of the STAT family in HNSC, and further study should be performed to verify these.

Introduction

Head and neck cancer (HNC) is a collection of malignant tumors occurring in the upper gastrointestinal tract, salivary glands, and thyroid [1]. Over 830,000 people are estimated to be diagnosed with HNC, and over 430,000 people are estimated to die of HNC annually globally [2]. About 90% of HNCs are head and neck squamous cell carcinomas (HNSC) [3]. Though aggressive therapies, including surgery, chemotherapy, and immunotherapy, were applied for HNSC, over 50% curative patients were present with relapse [4]. Worse still, the mortality of HNSC is as high as 40–50% [5]. Once HNSC patients present with recurrence and/or metastasis, the median overall survival (OS) hardly exceeds 12 months [6]. These sobering findings demonstrate an urgent need for novel approaches to HNSC.

STAT proteins are implicated in various biological processes, including cell proliferation, metastasis, and immune regulation [7]. Seven members have been identified, including STAT1/2/3/4/5A/5B/6. Data increasingly reveal that variant STAT proteins and abnormally activated STAT pathways are linked to various diseases, such as malignancies, asthma and immune-related disease [7, 8]. Some proteins of the STAT family were suggested as therapy targets for certain cancers due to their significance in tumor initiation and progression [9]. Moreover, some proteins of the STAT family were also suggested as the biomarkers for the diagnosis and prognosis of cancers, including STAT1 and STAT2 for pancreatic cancer and STAT5B and STAT6 for lung cancer [10, 11].

Several studies have been performed to clarify the expression or the functions of certain STAT family members in HNSC. For example, inhibition of STAT3 could lead to greater cetuximab sensitivity [12]. Activation of STAT4 could potentially mitigate lymphatic metastasis in HNSC [13]. Moreover, gene-expression signature associated with recur-

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rent disease in HNSC was profiled to clarify the gene expression profile of HNSC[14]. However, the role of the STAT family in HNSC was far from fully illuminated. Therefore, we will systematically explore and analyze STAT family expression and their diagnostic and prognostic value, as well as their related regulatory networks in HNSC. Our findings will provide additional data about the significant function of the STAT family in the tumorigenesis and progress of HNSC.

**Methods**

**Patient information and datasets**

Gene expression HNSC dataset GSE2379 [15] of Oncomine was extracted and analyzed in our study (May 8, 2020). The gene expression profiles (level 3 data) of primary HNSC patients were extracted from the TCGA database (https://tcga-data.nci.nih.gov/tcga/) (May 8, 2020). Clinical data such as gender, age, survival, and outcome were also downloaded from the TCGA data portal. Further analyses were performed with following bioinformatics analysis portals (TCGA visualization portals).

**Oncomine**

Oncomine (https://www.oncomine.org/) is a cancer microarray database which could be used for gene-expression profiles mining [16]. The mRNA level of the STAT family in HNSC patients and healthy people was analyzed using Oncomine. The fold-change was set as 2, and the P-value was set as 0.05.

**UALCAN**

UALCAN (http://ualcan.path.uab.edu/index.html) is the Cancer Genome Atlas (TCGA) database visual web portal [17]. The mRNA level of the STAT family in HNSC patients and healthy people and its correlation with clinical pathological parameters, including gender and tumor stage, was analyzed using UALCAN. These analyses were performed using TCGA HNSC dataset (n = 520), and p-value <0.05 indicated that the results were statistically significant.

**Kaplan Meier-plotter**

Kaplan Meier-plotter (KM-plotter, http://www.kmplot.com/) is a comprehensive meta-analysis web port for the discovery and validation of survival biomarkers [18]. The role of the STAT family in the prognosis of HNSC patients was analyzed using the KM-plotter with the medium STAT family expression as the group cut-off value. These analyses were performed using the TCGA HNSC dataset (n = 520), and p-value <0.05 indicated that the results were statistically significant.

**cbioportal**

cbioportal (https://www.cbioportal.org/) is a TCGA database visual web portal for genomics analysis [19]. The genetic alteration
Table 1

| TLR  | Fold Change | P value | t-test | Reference      |
|------|-------------|---------|--------|----------------|
| STAT1 | 3.090 3.104 | 9.25E-12 | 0.001  | 8.874 6.681    | PMID:14729608 PMID: 14676830 |
| STAT2 | NA          | NA      | NA     | NA             | NA          |
| STAT3 | NA          | NA      | NA     | NA             | NA          |
| STAT4 | NA          | NA      | NA     | NA             | NA          |
| STAT5A| NA         | NA      | NA     | NA             | NA          |
| STAT5B| NA         | NA      | NA     | NA             | NA          |
| STAT6 | NA          | NA      | NA     | NA             | NA          |

Fig 2. STAT family level in HNSC. The relative level of STAT1(A), STAT2 (B), STAT3(C), STAT4(D), STAT5A(E), STAT5B(F), and STAT6(G) in HNSC tissues and normal tissues.

and gene co-expression of STAT family in HNSC were explored with cBioportal using the TCGA HNSC dataset (n = 520). Mutation data were obtained from whole exome sequencing. Mutation packager: HNSC/20160128/gdac.broadinstitute.org_HNSC.Mutation_Packager_Raw.Calls.Level.3.2016012800.0.0.tar.gz. Genomic alterations of the STAT family in HNSC, including mutations, CNAs (amplifications and homozygous deletions), and changes in gene expression or protein abundance, were analyzed. We also analyzed the effects of genetic alteration of the STAT family on patients’ prognosis in the “survival” module of cBioportal. p-value < 0.05 indicated that the results were statistically significant.

**TIMER**

TIMER (http://cistrome.org/TIMER/) is a TCGA database visual web portal for analyses of tumor immunity [20]. The correlation analysis between STAT5A with immune cells infiltrations (“Gene” module) as well as immune biomarker level (“correlation” module) in HNSC were acquired in TIMER, which is performed by spearman analysis. These analyses were performed using the TCGA HNSC dataset (n = 520), and p-value < 0.05 indicated that the results were statistically significant.

**Linkedomics**

LinkedOmics (http://www.linkedomics.org/login.php) is a TCGA database visual web portal for genomics analysis [21]. The genes significantly correlated with STAT5A in HNSC were explored with the “Link-Finder” module using Spearman’s correlation coefficient. Moreover, the enrichment analyses, including those of GO, KEGG pathways, kinase targets, miRNA targets and transcription factor-targets of STAT5A, and correlated genes, were explored with the “Link-Interpreter” module using GSEA analysis. The “Link-Interpreter” module of LinkedOmics could perform pathway and network analyses of differentially expressed genes. Web-based GeneSeT AnAlysis Toolkit (WebGestalt) is one of the most comprehensive functional category databases [22]. These analyses were performed using the TCGA HNSC dataset (n = 520). The rank criterion was an FDR < 0.05, and 500 simulations were performed.

**Result**

**Defining the STAT family in HNSC**

The mRNA level of STAT family in HNSC was got from Oncomine and UALCAN. As shown in Fig. 1, the data of Oncomine revealed that the mRNA level of STAT family was increased or decreased in different types of cancers, including HNSC. Ginoset et al. found that the STAT1 mRNA level was upregulated with a fold-change of 3.090 (P = 9.25E-11, Table 1) [14]. Another study also revealed that the STAT1 mRNA level was 3.104 times in tumor tissues compared with normal tissues [15]. However, there is no data about the expression of the other STAT family proteins. According to the data from UALCAN, the mRNA level of STAT1 (Fig. 2A, P = 1.62E-12), STAT2 (Fig. 2B, P = 1.62E-12), STAT4 (Fig. 2D, P = 2.69E-4), STAT5A (Fig. 2E, P = 2.05E-4), and STAT6 (Fig. 2G, P = 1.37E-4) were significantly upregulated in HNSC tissues.

**The expression of the STAT family in subgroup group of HNSC patients**

The above data suggest that STAT1/2/4/5A/6 were significantly up-regulated in HNSC tissues. Thus, we further detected the correlation between the STAT family and clinical pathological features in HNSC. The pathological features were comprised of race, gender, age, tumor grade, HPV status, nodal metastasis status, TP53 mutation status, and cancer stage. As expected, STAT1 and STAT2 were upregulated in HNSC patients in contrast to healthy individuals in subgroup analyses based...
Fig 3. The prognostic value of the STAT family in HNSC. (A) The overall survival curve of HNSC patients with high and low level of the STAT family. (B) The relapse-free survival curve of HNSC patients with high and low level of STAT family.

Fig 4. Co-expression and genetic alteration analysis of the STAT family in HNSC. (A) Co-expression heat map of STAT family in HNSC. (B) Summary of alterations of STAT family in HNSC. (C,D) Kaplan–Meier plots comparing disease-free survival and overall survival in cases with/without STAT family alterations.
on race, gender, age, tumor grade, HPV status, nodal metastasis status, TP53 mutation status, and cancer stage (Supplemental Fig. 1). Interestingly, the mRNA level of STAT4 (Supplemental Fig. 2A), STAT5A (Supplemental Fig. 2B), and STAT6 (Supplemental Fig. 2C) were upregulated in HNSC patients in contrast to healthy individuals in subgroup analyses. Therefore, the levels of STAT1/2/4/5A/6 could be used for the detection of HNSC.

**Prognostic value of the STAT family in HNSC**

The prognostic value of different expressed STAT family in HNSC were analyzed with KM-plotter. The results demonstrated that HNSC patients with high level of STAT5A (HR=1.51, 95%CI:1.15–1.97, P = 0.0026) had a poor overall survival (OS) (Fig. 3A). Interestingly, we found that HNSC patients with a high level of STAT5A (HR=2.15, 95%CI:0.97–4.76, P = 0.053) had a poor relapse-free survival (RFS); however, the P-value is over 0.05 (Fig. 3B). Further, STAT1/2/4/6 had no effect on the OS and RFS of HNSC patients. Therefore, the level of STAT5A could be used for predicting the prognosis of HNSC patients.

**Co-expression and genetic alteration of the STAT family in HNSC**

Fig. 4A shows the result of co-expression of the STAT family in HNSC. A moderate to high correlation was obtained in the STAT family. Genetic alteration revealed that STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 were altered in 6%, 5%, 7%, 8%, 6%, 6%, and 4% of the queried TCGA HNSC samples, respectively (Fig. 4B). Further, genetic alteration forms of the STAT family were composed of missense mutation, truncating mutation, amplification, deep deletion, mRNA high, mRNA low, protein high and protein low (Fig. 4B). However, these genetic alterations would not affect the OS (Fig. 4C, P = 0.547) and disease-free survival (Fig. 4D, P = 0.700) of HNSC patients.

**Immune infiltrations analysis of STAT5A in HNSC**

The above results revealed that STAT5A level was increased in HNSC tissues and correlated with clinical pathological features. Moreover, the level of STAT5A could be used for predicting the prognosis of HNSC patients. Therefore, STAT5A was selected for further analysis. Previous studies have suggested the significance of STAT signaling...
in immunology [23]. Here, we conducted immune infiltrations analysis of STAT5A in HNSC. The data suggested a significant association between STAT5A expression and the abundance of B cells (Cor=0.381, \( P = 6.62e-18 \)), CD8+ T cells (Cor=0.481, \( P = 7.70e-29 \)), CD4+ T cells (Cor=0.569, \( P = 1.48e-42 \)), Macrophages (Cor=0.476, \( P = 1.10e-28 \)), Neutrophils (Cor=0.573, \( P = 3.30e-43 \)), and Dendritic cells (Cor=0.594, \( P = 2.78e-47 \)) (Fig. 5A). Additionally, we also found that copy number alteration of STAT5A could certainly inhibit infiltration level (Fig. 5B). Interestingly, there is a close correlation between STAT5A level and the expression of immune markers in HNSC (Table 2). Therefore, STAT5A may exert a specific function in immune infiltration of HNSC microenvironment.

### Kinase targets and transcription factor targets of STAT5A in HNSC

The above results suggested a significant role of STAT5A in HNSC. Thus, we further explored the Kinase targets and transcription factor (TF) targets of STAT5A in HNSC. As shown in Table 3, the most significant five Kinase targets of STAT5A in HNSC are Kinase_LCK, Kinase_SYK, Kinase_TYN, Kinase_LYN, and Kinase_BCR. Moreover, the gene sets enriched for kinase LCK are mainly linked to antigen receptor-mediated signaling pathway, immune response, T cell receptor signaling pathway, and T cell activation (Fig. 6). With regard to the TF targets of STAT5A in HNSC, the results suggested VSIRF_Q6, VSELF1_Q6, VSPU1_Q6, VSPEA3_Q6, and VSIRF_Q6 as the top 5 significant targets.

| Immune cells | Biomarkers | None Cor | P-value | Purity Cor | P-value |
|--------------|------------|----------|---------|------------|---------|
| CD8+ T cell  | CD6A       | 0.593    | ***     | 0.585      | ***     |
|             | CD8B       | 0.595    | ***     | 0.584      | ***     |
| T cell (general) | CD3D     | 0.621    | ***     | 0.616      | ***     |
|             | CD3E       | 0.66     | ***     | 0.655      | ***     |
| B cell      | CD19       | 0.465    | ***     | 0.448      | ***     |
|             | CD79A      | 0.448    | ***     | 0.43       | ***     |
| Monocyte    | CD86       | 0.542    | ***     | 0.527      | ***     |
|             | CD115(CSF1R) | 0.597 | ***     | 0.585      | ***     |
| TAM         | CCL2       | 0.451    | ***     | 0.434      | ***     |
|             | CD68       | 0.297    | ***     | 0.282      | ***     |
| M1 Macrophage | IL10    | 0.408    | ***     | 0.39       | ***     |
|             | INOS (NOS2) | 0.289 | ***     | 0.288      | ***     |
|             | IFR5       | 0.409    | ***     | 0.416      | ***     |
|             | COX2(PTGS2) | −0.042 | 0.344    | −0.033     | 0.464   |
| M2 Macrophage | CD163     | 0.451    | ***     | 0.443      | ***     |
|             | VSG4       | 0.403    | ***     | 0.393      | ***     |
|             | M54A4A     | 0.468    | ***     | 0.455      | ***     |
| Neutrophils | CD669 (CEACAM8) | 0.089 | *     | 0.059, 0.191 |     |
|             | CD11b (ITGAM) | 0.515 | **     | 0.492      | ***     |
|             | CCR7       | 0.57     | ***     | 0.566      | ***     |
| Natural killer cell | KIR2DL1 | 0.256    | ***     | 0.264      | ***     |
|             | KIR2DL3    | 0.377    | ***     | 0.371      | ***     |
|             | KIR2DL4    | 0.442    | ***     | 0.443      | ***     |
|             | KIR3DL1    | 0.346    | ***     | 0.314      | ***     |
|             | KIR3DL2    | 0.487    | ***     | 0.482      | ***     |
|             | KIR3DL3    | 0.232    | ***     | 0.22       | ***     |
|             | KIR2DS4    | 0.28     | ***     | 0.264      | ***     |
| Dendritic cell | HLA-DPB1  | 0.632    | ***     | 0.624      | ***     |
|             | HLA-DQB1   | 0.493    | ***     | 0.473      | ***     |
|             | HLA-DRB1   | 0.611    | ***     | 0.601      | ***     |
|             | HLA-DPA1   | 0.62     | ***     | 0.609      | ***     |
| Th1         | T-bet (TBX21) | 0.623 | ***     | 0.611      | ***     |
|             | STAT4      | 0.537    | ***     | 0.528      | ***     |
|             | STAT1      | 0.397    | ***     | 0.388      | ***     |
|             | IFN-γ (IFNG) | 0.479 | ***     | 0.463      | ***     |
|             | TNF-α (TNF) | 0.269 | ***     | 0.255      | ***     |
| Th2         | GATA3      | 0.345    | ***     | 0.333      | ***     |
|             | STAT6      | 0.361    | ***     | 0.387      | ***     |
|             | STAT5A     | -        | -       | -          | -       |
|             | IL13       | 0.373    | ***     | 0.365      | ***     |
| Th            | BC16      | 0.206    | ***     | 0.231      | ***     |
|             | IL21       | 0.445    | ***     | 0.424      | ***     |
| Th17         | STAT3      | 0.494    | ***     | 0.494      | ***     |
|             | IL17A      | 0.273    | ***     | 0.258      | ***     |
| Treg         | FOXP3      | 0.618    | ***     | 0.607      | ***     |
|             | CCR8       | 0.52     | ***     | 0.501      | ***     |
|             | STAT5B     | 0.574    | ***     | 0.575      | ***     |
| T cell exhaustion | TGFβ(TGFβ1) | 0.014 | 0.752    | −0.003     | 0.944   |
|             | PD-1 (PDCD1) | 0.621 | ***     | 0.613      | ***     |
|             | CTLA4      | 0.574    | ***     | 0.567      | ***     |
|             | LAG3       | 0.568    | ***     | 0.562      | ***     |
|             | TIM-3 (HAVCR2) | 0.603 | ***     | 0.592      | ***     |
|             | GZMB       | 0.52     | ***     | 0.509      | ***     |
Interestingly, the gene sets enriched for TF VSIRF_Q6 are mainly linked to immune response, antigen receptor-mediated signaling pathway, T cell receptor signaling pathway, T cell activation, and leukocyte differentiation (Fig. 7).

**Enrichment analysis of STAT5A in HNSC**

The above results suggested a significant role of STAT5A in HNSC. Thus, we conducted enrichment analysis of STAT5A in HNSC. We first explored co-expression genes correlated with STAT5A with the data of TCGA HNSC patients with LinkedOmics. The results in a volcano plot found that 10,151 genes were correlated with STAT5A were obtained in HNSC, including 6132 genes that were positively linked to STAT5A and 4042 genes that were negatively linked to STAT5A (Fig. 8A). The heat map in Fig. 8B and C shows the 50 significant gene sets positively and negatively linked to STAT5A (Fig. 8B and C). GO analysis conducted by GSEA suggested that STAT5A and co-expression genes were mainly responsible for adaptive immune response, T cell activation, leukocyte proliferation, rRNA metabolic process, cytokine receptor binding and activity, translation factor activity, antigen binding, and immunoglobulin binding (Fig. 8D–F). Further, KEGG analysis conducted by GSEA suggested that STAT5A and co-expression genes were mainly responsible for cytokine-cytokine receptor interaction, chemokine signaling pathway, cell adhesion molecules, ribosome, Th17 cell differentiation, and RNA transport (Fig. 8G).

**Discussion**

The STAT family has been found to be involved in human cancer tumorigenesis, progression, metastasis, survival, and resistance to treat-
In gastric cancer, STAT5A could facilitate the tumorigenesis of tumor cells [25]. STAT3 was suggested as a novel drug target for cancer therapy [26]. In HNSC, inhibition of STAT3 could lead to greater cetuximab sensitivity [12]. Moreover, activation of STAT4 could potentially mitigate lymphatic metastasis in HNSC [13]. However, the role of STAT family in HNSC was far from fully illuminated. Therefore, our study was performed.

The level of STAT family in HNSC was first detected, which suggested that the mRNA levels of STAT1/2/4/5A/6 were significantly upregulated in HNSC tissues. We also found that the level of STAT1/2/4/5A/6 could be used for the detection of HNSC. Moreover, HNSC patients with high levels of STAT5A had a poor overall survival and relapse-free survival. As a matter of fact, some of the STAT family had been found to be as biomarkers for cancers. In breast cancer, individual STATs may function as a biomarker predicting favorable prognosis [27]. Pang et al. found that STAT2 was a marker significantly associated with the prognosis of pancreatic cancer [11]. Moreover, high STAT4 level demonstrated a better disease-free survival in gastric cancer [28].

Another important finding of our study was that STAT5A was associated with immune cell infiltrations and that copy number alteration of STAT5A could certainly inhibit infiltration level. Our result was consistent with previous data. Rani et al. found that STAT5A was involved in the development of Tregs [29]. Moreover, sustained activation of STAT5A was linked to anti-tumor immunosuppression [29]. In hepatocellular carcinoma, STAT5A was associated with immune-related biological processes [30]. In fact, certain immune cells or immune biomarkers associated with STAT5A had been suggested as the immune-therapy targets for HNSC. PD-L1 expression could predict benefit from checkpoint inhibitor therapy in HNSC [31]. Another study demonstrated CTLA4 as a novel therapeutic strategy in HNSCC [31].

Fig 7. PPI network of transcription factor IRF networks. PPI network and functional analysis about the gene sets of transcription factor IRF networks. The different colors for the network nodes indicate the biological functions of the set of enrichment genes.
Therefore, STAT5A may exert a specific function in immune infiltration of HNSC microenvironment.

Several kinases targets, including Kinase_LCK, Kinase_SYK, Kinase_TYN, Kinase_LYN, and Kinase_BCR, were also identified. Interestingly, these kinases were associated with cell-cycle arrest, apoptosis, mitosis, and immune response [32–34]. Additionally, kinase LCK is a positive regulator of inflammatory signaling and is suggested as the potential target for cancer treatment [35]. Moreover, LCK is the major contributor to the development and activation of T-cells [36]. Thus, STAT5A regulated immune infiltration in HNSC through kinase LCK.

We also identified several transcription factor targets of STAT5A in HNSC, including V$IRF_Q6, V$SELF1_Q6, V$PU1_Q6, V$PEA3_Q6, and V$IRF_Q6. These transcription factor targets in tumor cells could result in cell cycle disorder and affect cell aberrant proliferation, decreased differentiation, decreased apoptosis, and rapid multiplication and development [37]. In nasopharyngeal carcinoma, ELFI1 could promote tumor cell proliferation and metastasis [38]. In colorectal carcinoma, Pea3 facilitate tumor cell invasion and metastasis. However, these transcription factor targets have rarely been studied in HNSC. Therefore, STAT5A and these transcription factors may also regulate cell proliferation and invasion in HNSC.

There are some limitations in this study. The sample data were basically derived from the TCGA database, and it would be better to verify the result with other databases. In addition, we did not perform experimental verification.

Conclusion

Overall, our results provided additional data for the expression and clinical significance of the STAT family in HNSC, and further study should be performed to verify these findings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

**Haosheng Ni:** Data curation, Formal analysis, Visualization, Writing - original draft. **Hui Sun:** Data curation, Formal analysis, Visualization, Writing - original draft. **Miaosen Zheng:** Methodology. **Tingting Bian:**
Software. Jian Li: Investigation, Project administration, Resources.
Xiaoli Li: Validation. Jinguo Zhang: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. Yifei Li: Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

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Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2020.100976.

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