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REVIEW

SOCS1 and its Potential Clinical Role in Tumor

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Abstract
Suppressor of cytokine signaling1 (SOCS1), as a member of SOCS family, has been widely studied in recent years. It has been found that SOCS1 not only participates in cell signaling, but also in ubiquitination mediated protein degradation process. Both of these two functions play an important role in the growth and proliferation of cells. Therefore, researchers speculated that SOCS1 also played an important role in tumors. This review mainly focuses on the structure, transcriptional regulation and functions of SOCS1 protein, and finally describes the possible clinical role of SOCS1 protein in tumors.

Keywords SOCS1 · Cell signaling · Ubiquitination · Tumors

Introduction

Cytokines bind to their specific receptors on the surface of cell to transduce biological information to target cells. Their related signaling pathways control and regulate fundamental biological processes including hematopoiesis, inflammation, immunity and the development of tumor [1]. Suppressors of cytkine signalling (SOCS) proteins are modulators of cytokine and growth factor signaling whose aberrant regulation have been linked to a variety of disease. Among them, SOCS1 has been extensively investigated. Initially, it was recognized as a negative feedback regulator of cytokine signaling, for example, the Janus kinases–signal transducers and activators of transcription (JAK–STAT) signaling pathway, which is important in cellular activation, proliferation, and differentiation [2]. Then it has been found that SOCS1 was also involved in E3 ubiquitin ligases complex, acting as substrate-recognition modules to mediate the polyubiquitination and subsequent degradation of substrate proteins which may be the key components of cytokine signal transduction pathways [3]. Both two functions of SOC1 are very important to regulate the growth and proliferation of cell. Therefore, numerous studies have speculated that SOCS1 may play a role in regulating tumor growth and proliferation, such as hepatocellular carcinoma [4, 5], melanoma [6, 7], gastric cancer [8] prostate cancer [9] and so on. In this review, we mainly describe the structure, regulation of SOCS1 and its role in cell signaling and ubiquitination. Then we focus on the reported potential clinical role of SOCS1 in tumor.

Structure of SOCS Family

As so far, eight members of SOCS protein family are identified, they are SOCS1–7 and CIS(cytokine-inducible SH2-containing protein). As reported, they contain a typical C-terminal SOCS box motif, a central SH2-domain and an N-terminal domain of variable length and sequence. Among them, SOCS1-SOCS3 and CIS had higher similarity not only in sctructure but also in function. Apart from SOCS4–7 which had long N- terminal domains, they had short N- terminal domains. SOCS1-SOCS3 and CIS are induced by cytokines. But regarding SOCS4–7, their functions have not been identified clearly yet.

The SOCS box of SOCS family is a 40-amino acid motif, which functions to recruit an E3 ubiquitin ligase complex consisting of the adapter proteins elongins B and C, Rbx2 and the scaffold protein Cullin5. So the SOCS box-

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containing proteins are thought to act as substrate-recognition modules to mediate the polyubiquitination and subsequent degradation of substrate proteins by the 26S proteasome [10]. There are two core interaction sites identified in the SOCS box: the BC-box and the Cul-box. The BC-box is a conserved N-terminal region of 12 residues, responsible for recruiting elongins B and C. This recruiting is mainly through the highly conserved leucine in the +4 position in the BC-box [11, 12]. The Cul-box was in the C-terminal of SOCS proteins, mediating Cullin5 binding via an "LPXP" motif [13].

The SH2 domain of SOCS proteins has an N-terminal-helix termed the extended SH2 subdomain (ESS), which functions to stable the phosphotyrosine-binding loop. It can bind to phosphorylated residues of the receptor complex, folding the SOCS box-associated E3 ubiquitin ligase so that it can recognize its substrate [14, 15]. Hence, the SH2 domain may act as a determinant of the target which the SOCS proteins bind to. As reported, the SH2 domain of SOCS1 determined it could binds to the activation loop of JAKs [16]. But in the CIS, SOCS2, and SOCS3 proteins, SH2 domain bind to phosphorylated tyrosine residues of the activated cytokine receptors. Additinally, only SOCS1 and SOCS3 in SOCS family have a unique N-terminal motif named KIR (kinase inhibitory region) domain which is a 12-residue motif that functions to inhibit JAK tyrosine kinase activity. It is reported that KIR domain of SOCS3 occludes the substrate-binding groove on JAK2, blacking substrate association [17, 18]. So the KIR domain might function as a pseudosubstrate of JAKs, which is essential for the suppression of cytokine signal. However, it needs more confirmation in SOCS1 protein.

Summarily, according to the structure of SOCS1 protein, its functions is mainly divided into two parts: Firstly, as a signal inhibitor, it can inhibit the transmission of cell signal, regulating proliferation and apoptosis of cell; secondly, as a small part to join in the process of ubiquitination, mediating the degradation of ubiquitinated substrates to regulate the growth of the cells.

SOCS1 and its Regulation

As reported, the SOCS1 gene in humans located on 16p13.3 and codes for a protein with 211 amino acids [19]. It is highly conserved among various species, including human, chimpanzee, dog, cow, rat and chicken [19].

The transcriptional regulation of SOCS1 is mainly reported in three aspects: Firstly, it can be regulated by the cell signal factors: the promoter of SOCS1 contains STAT binding region, which can be regulated by STAT signaling factors. Its specific mechanism is as follows: cytokine binds to the receptor to induce its oligomerization. Then oligomerizatied receptor facilitates cross-phosphorylation and activation of the receptor-bound JAK kinases. JAKs phosphorylate receptor tyrosines to recruit and activate STATs. Activated STATs dimerize and translocate into the nucleus to induce the expression of SOCS1 [20]. But interestingly, SOCS1 protein can bind to the activation loop tyrosine residues of JAKs and inhibits their activity, interrupting the JAK–STAT pathway, negatively regulating itself expression. Then, it was also reported that the SOCS1's promoter is actively repressed by growth factor independence-1B (GFI-1B) transcriptional repressor. Erythropoietin (EPO) stimulation downmodulates GFI-1B expression in EPO-responsive cell lines, allowing transcriptional activation of SOCS1 [21]. SOCS1 can also be induced by other cell signal factors, such as IL-2 [2, 22], IL-3 [2], IL-4 [20, 23–26], IL-6 [20, 27], IL-13 [26], interferon-γ (IFN-γ) [28, 29], IFN-α/β [30, 31], EPO [2, 27], G-CSF [20], leukemia inhibitory factor (LIF) [20], and growth hormone (GH) [32, 33] and so on.

Secondly, its expression was regulated by the methylation levels of its promoter: Studies have ascertained that the promoter of SOCS1 is located on the CpG island of the 5′-end this gene, and its abnormal methylation can result in silencing of SOCS1 expression [34].

Thirdly, its expression level was also regulated by post-translational modification. It has been found that SOCS box played a role in maintaining SOCS1 stability. In vitro overexpression studies [35] have demonstrated that deletion of the SOCS box decreases the half-life of SOCS-1 leading to the suggestion that a major role for the interaction of the SOCS box with elongins B and C is to stabilize the SOCS protein [11]. But controversially, another study group observed that mutations within the SOCS box that destabilize the interaction between SOCS1 and Elongin BC prevented SOCS1 degradation [36], it was suspected that Elongin BC may be targeting SOCS1 to proteasomal degradation. Besides above findings, there is another finding that SOCS1 could bind to TRIM8/GERP which is a Ring finger protein, and this interaction facilitates SOCS1 degradation [37].

What's more, it has been found that miRNAs may also play a role in post-translational modification of SOCS1. It was found that miR-221-5p could regulate SOCS1 expression through targeted its 3'UTR to regulate the proliferation, migration of prostate cancer cells in vitro and tumorigenesis in vivo [9]. Then, another group found that miR-155 could regulate SOCS1 expression by the same mechanism. It reported that SOCS1 protein expression was increased when miR-155 in mouse osteoblastic cells was knocked down, and it was suppressed when osteoblastic cells was transfected with miR-155 [38]. This phenomenon was also proved in T cell by another group which found that FOXP3 contributes to the maintenance of SOCS1 levels by negatively regulating miR-155 in T cells [39].

So far, many studies have been carried out on SOCS1. But it still needs more researches on the detailed regulation

mechanism of SOCS1 which may play an important role in understanding the role of SOCS1 in diseases.

The Role of SOCS1 in Cell Signaling

There are mainly two pathways SOCS1 involved in: one is JAK/STAT signaling pathway, the other is TLR signaling. The JAK–STAT pathway is an essential intracellular mechanism of cytokines that regulates gene expression, cellular activation, proliferation, and differentiation [40]. It was activated by the cytokines receptor aggregation and trans-phosphorylation. Activated JAKs can phosphorylate tyrosine residues in the cytoplasmic domain of cytokine receptors, creating recruitment sites for Src-homology 2 (SH2) domain of STATs proteins. Then phosphorylated STATs dimerize and translocate into nucleus to induce transcription of cytokine-responsive genes, which mediates specific cellular functions [41].

In JAK/STAT signaling pathway, SOCS1 can interact directly with the kinase domain (JH1) of JAKs, including JAK1, JAK2, JAK3, and Tyk2, via its ESS and KIR domains, inhibiing their kinase activation and catalytic activity. Then the downstream substrates such as the STAT proteins' phosphorylation and activation were interrupted [2, 42, 43]. This results in the termination or attenuation of JAK-mediated signaling, which is crucial in the proliferation, differentiation and survival of cells.

Lipopolysaccharide (LPS) is an integral cell wall component of Gram-negative bacteria and can provoke a life-threatening condition called endotoxic shock [44]. It was recognized by a member of Toll-like receptors (TLRs) which is essential for the recognition of specific patterns of microbial components [45–47]. Activation of TLRs by LPS would induce responses of host innate immune cells to LPS. But sometimes this response was excessive, causing various tissue damage, circulatory failure, and occasionally death of host [44]. So down-regulating TLR signaling would ensure host have a safety responses to LPS and/or unresponsiveness to a second stimulation with LPS [48]. Then it has been found that SOCS1 play a role in down-regulating TLR signaling [34]. The mechanisms underlying SOCS1 regulating TLR signaling could be divided into two categories. The one is SOCS1 can down-regulate the TLR signaling by interference with the JAK/STAT pathway which was activated by the initial TLR activation. The other is SOCS1 can interact with TLR adaptor proteins such as MAL and IRAK [34, 49, 50] for degradation, as well as attenuate cytokine signaling activated by initial TLR stimulation. However, it's interestingly that SOCS1 can also be induced indirectly through cytokines induced by initial TLR activation, such as IL-6 and INF-b [51]. Therefore, SOCS1 is involved in a negative feedback regulation in the TLR signaling. However, whether similar mechanisms of SOCS1-mediated regulation of TLR signaling occur in different cell lineages are still unclear and need further investigations.

The Role of SOCS1 in Ubquitination

As previously described, SOCS box could recruit E3 ubiquitin ligases complex, acting as substrate-recognition modules to mediate the polyubiquitination and subsequent degradation of substrate proteins by the 26S proteasome. Therefore the main role of SOCS1 is acting as the substrate recruitment modules of E3 ubiquitin ligases (or elonginBC-cullin5 ubiquitin ligase).

It has now been shown that the SOCS box is only partially folded in the absence of elongins B and C and that their presence is required to stabilise the protein [12]. However, in comparison to the other six family members, the SOCS box of SOCS1 bound with weaker affinity to cullin5 [52]. There is now direct evidence that SOCS1 can act as the substrate recognition component of an ECS-type E3 ubiquitin ligase complex to regulate the half-life of Vav [53] and TEL/JAK2 fusion protein [54, 55]. But interestingly, SOCS1 only binds to the substrates which have been posttranslationally modified. For example, when SOCS1 binds to JAKs and other potential substrates, it requires their prior activation by phosphorylation on specific tyrosine residues [43, 56, 57]. And as reported, SOCS proteins recruit substrates for lysine-48 linked ubiquitination, targeting those substrates for proteasomal degradation [58]. But on the other hand, signal transduction can be prolonged for some cytokines in the presence of proteasome inhibitors [59, 60]. However, in in-vitro overexpression studies, deletion of the SOCS box from SOCS1 had little impact on the inhibition of cytokine signal transduction [35, 43]. Therefore, it requires more research to study whether SOCS1 is involved in the ubiquitination degradation process of cell signal factors.

Recently, it has been found CUEDC2 which is a novel interacting partner of the SOCS1 protein to suppress SOCS1's ubiquity-mediated degradation, JAK1-STAT3 pathway activation and leukaemogenesis of AML [61]. This implies that the anti-caking agent of SOCS1, may inhibit SOCS1-mediated ubiquitination degradation process to inhibit the progression of diseases.

Methlytion of SOCS1 in Tumors

As studies showed, SOCS1 often keeps hypermethylation in tumors. And its methylation level is often related to the clinical characteristics of tumors.

Several studies found that the promoters of SOCS1 were often hypermethylation in hepatocellular carcinoma. Okochi

O. et al. found that hypermethylation of SOCS1 detected in 30 of 50 (60%) HCC specimens and this was more obviously in HCC derived from liver cirrhosis ($P = 0.0207$) when they analyzed the correlation between the clinic pathological data and SOCS-1 aberrant methylation [4]. Then Chu PY et al. approved this results when they analysis the methylation status of CpG sites at the promoter region of SOCS1 in HCC samples. Their further study revealed that the promoter methylation of SOCS1 not only was correlated with HCC derived from liver cirrhosis ($p = 0.044$) but also with tumour size ($p = 0.038$) [5]. At the same time, another group found hypermethylation of SOCS1 in hepatocellular carcinoma after liver transplantation often had a significantly worse recurrence-free survival (RFS) [62]. Interestingly, there is also a group found that methylation status of SOCS1 could be as a clonal marker for multicentric hepatocellular carcinoma when it was used with other hypermethylated genes, such as p16, DAP-Kinase, GSTP1, APC, RIZ1, SFRP1, SFRP2, SFRP5, RUNX3 [63].

Then in gastric carcinoma, studies found that hypermethylation of the SOCS1 gene was detected in 33 (44%) of 75 gastric carcinoma (GC) tissues, but only in 3 (12%) of 25 corresponding nonneoplastic mucosae. And the methylation of the SOCS1 had a significantly correlation with the lymph node metastasis, advanced tumor stage and reduced expression of SOCS1 in GC tissues ($p = 0.009$, 0.034 and 0.002, respectively) [8]. These results suggest that inactivation of the SOCS1 gene may play an important role in development, progression and metastasis of GC, but it need more experiments to approve this.

What's more, the correlation between hypermethylation of the SOCS1 and tumor stages was also found in esophageal squamous cell carcinoma. Hussain S. and his team found aberrant promoter methylation of the SOCS1 gene was found in 45% of the esophageal tumor tissues, which was also found to be significantly associated with advanced stage of esophageal carcinoma ($P < 0.01$) [64]. Additionally, Sobti RC et al. found in cervical carcinoma, 61% of the tumor tissues showed aberrant promoter methylation of SOCS1, and this situation is significantly associated with severity of the disease ($p < 0.01$) [65]. Apart from above studies, hypermethylated SOCS1 were also found in 60% of acute myeloid leukemia (AML) [66, 67], 62.9%–75% of multiple myeloma (MM) [68, 69], 50% of pancreatic cancers [70], 75% of melanoma [71], 40% of hepatoblastoma [72].

In summary, the hypermethylation status of SOCS1 might be as a tumor suppressor in the progression of tumor. Related mechanism may because SOCS1 is a JAK/STAT inhibitor, regulating the JAK/STAT signal transduction pathway which is an important pathway that relays signals from various cytokines in the extracellular matrix into the cell. When SOCS1 was methylated, its expression was repressed, leading the JAK/STAT pathway to be active which was the main reason for the proliferation, migration of tumor cell [68, 70]. However, it still needs more studies to support this idea.

Potential Clinical Role of SOCS1 in Tumors

Now it has been discovered that the progress of tumors depends not only on the genetic mutation of malignant tumor cells, but also on the changes of tumor microenvironment such as matrix, blood vessels, infiltrating inflammatory cells. Then it has been shown that immunity and inflammation are the two core parts that constitute the tumor microenvironment. However, no matter immunity or inflammation, they are all have a relationship to the cytokines. Immune response would release cytokines, but excessive release of cytokines could lead to an inflammatory reaction. Then overreaction of inflammation is just the start of the cancer.

Therefore, SOCS1, as a suppressor of cytokines signaling protein, is considered to play an important role in in tumor suppression. It has been shown that SOCS-1 is an essential physiological inhibitor of IFN-gamma signaling. Mice lacking this gene die in the early postnatal period from a disease characterized by hyper-responsiveness to endogenous IFN-gamma. But when the SOCS1 knockout mice were crossed with IFN-γ, Stat1, Stat6 or IFN-α receptor 1 -deficient mice, this lethal phenomenon could be restored, but these deficient mice are prone to inflammatory diseases, support the idea that SOCS1 plays an important role in the body's inflammatory response [73]. Then DC cell-mediated anti-tumor immune response can be modulated by regulation of SOCS1 expression. Studies showed that SOCS1-silenced DCs induce stronger anti-tumor immunity [74–77]. SOCS1 also plays an important role in the regulation of regulatory T cells (Tregs), which has been shown to regulate antitumor immunity. It has been found that SOCS1-deficiency in Tregs resulted in strong enhancement of antitumor immunity (Takahashi et al., unpublished data, reviewed in [78]) Then researchers also obtained encouraging results by silencing SOCS1 in macrophages to confirm its antitumor immunity [79]. In addition to its anti-tumor immunity, SOCS1 also has other anti-tumor mechanism. The study found SOCS1 could inhibit the growth of prostate cancer cells by down-regulating the expression of cyclins and cyclin-dependent kinases. And SOCS1 can also induce cycle arrest in tumors [80, 81].

Accordingly, some anti-tumor strategies targeting SOCS1 have been developed. For example, demethylation drugs, such as DAC, can restore SOCS1 expression in tumor cells and may serve as a potential strategy for antitumor therapy [68]. And Gene therapy with SOCS1 for gastric cancer induces G2/M arrest and has an anti-tumor effect on peritoneal carcinomatosis [78]. However, although SOCS1 has anti-tumor potential, it needs more investigation to study the specific role of

SOCS1 in tumor which will help us to develop more useful anti-tumor strategies.

On the other hand, SOCS1 has the potential function to be used as a diagnostic marker for tumor. It has been demonstrated that higher expression of SOCS1 mRNA is associated with earlier tumor stage and better clinical outcome in breast cancer [82]. However, other reports indicate that the positivity and intensity of SOCS1 staining were associated with tumor progression, as indicated by tumor invasion, tumor thickness and stage of disease [6]. And reduced SOCS1 expression is associated with tumor invasion and angiogenesis to promote brain-homing melanoma cells metastasis to the brain [7]. Additionally, it has found that SOCS1 expression is undetectable in normal individuals but overexpression of SOCS1 mRNA is detected in 65% positive CML patients in total WBC and 60% in granulocytes at diagnosis. Overexpression of SOCS1 mRNA is associated with poor cytogenetic responses to IFN-α and shorter median PFS [83]. What's more, as mentioned in above part, the SOCS1 can also be used as a diagnostic marker for tumor with other genes [63]. All these studies indicate that SOCS1 may be used as a marker for diagnosis of tumor.

Conclusion

As the first member of SOCS protein family, the understanding of the structure and function of SOCS1 have been greatly extended. Recently, there have been more and more reports on the possible role of SOCS1 in tumors, but in these reports, the role of SOCS1 are uncertain. For example, some reports suggest silencing SOCS1 in tumor cells can improve the sensitivity of tumor cells to IFNs and inhibit the proliferation of tumor cells, But others show that by using demethylation drugs, such as DAC, to restore the expression of SOCS1 in tumor cells, one can restore the tumor-suppressive function of SOCS1 [34]. Therefore, further researches are still necessarily needed to fully reveal the complex mechanisms of action, interaction and compensation among SOCS1 and other SOCS proteins and between SOCS and other proteins. Understanding these may help us to understand its role in the pathophysiology of tumor and find the appropriate therapeutic strategies.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare no conflict of interest.

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