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SOCS1 AND SOCS3: POTENTIAL CHEMOTHERAPEUTIC TARGETS FOR HUMAN PROSTATE CANCER

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ABSTRACT

Despite recent advances in early screening and chemotherapeutic intervention, prostate cancer remains a leading cause of cancer-related deaths in men in the United States. Thus, there exists a critical need to investigate and develop novel molecular strategies for the treatment of prostate cancer. Recent data revealed that suppressor of cytokine signaling proteins, SOCS1 and SOCS3, are potentially promising targets for the treatment of prostate cancer. Suppressor of cytokine signaling proteins are a family of negative feedback regulators that inhibit signal transduction pathways following activation from numerous cytokines, growth factors, and hormones. Additional studies are needed to reveal underlying genetic interactions controlling the anticancer effects observed in the experimental investigations highlighted in this review. The current review article is designed to focus on contemporary experimental evidence demonstrating the clinical significance of SOCS1 and SOCS3 in prostate cancer. Future research focusing on SOCS1 and SOCS3may elucidate officinal strategies to effectively attenuate prostate cancer cell growth.

Keywords: SOCS1, SOCS3, Negative regulator, Signal transduction, Prostate cancer

Abbreviations:SOCS1: Suppressor of cytokine signaling 1; SOCS3: Suppressor of cytokine signaling 3; ACS: American Cancer Society; JAK-STAT: Janus kinase-Signal transducer and

activator of transcription; MAPK: Mitogen-activated protein kinase; IL: Interleukin; G-GSF: Granulocytecolony-stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; LIF: Leukemia inhibitory factor; IFNα: Interferon alpha, IFNγ: Interferon gamma; EGF: Epidermal growth factor; EPO: Erythropoietin; SH2: Src Homology 2; CIS: Cytokine-inducible SH2 protein; KIR: Kinase inhibitory region; ESS: Extended SH2 domain; LNCaP: Lymph node carcinoma of the prostate; SCID: severely compromised immunodeficient; BPH: Benign prostatic hyperplasia; ZFP36: Zinc finger protein 36 homolog; FGF-2: Fibroblast growth factor2; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand

INTRODUCTION

Prostate cancer is a major health threat worldwide and remains the second leading cause of cancer-related deaths of men in the United States. Although it was recently reported that the cancer death rate in the United States has declined by 26% since 1991, according to the American Cancer Society, over 1.7 million people will be diagnosed with cancer in 2018. Moreover, the ACS estimates that approximately 609,000 Americans will die from cancer or cancer-related deaths this year (1). While the precise etiological factors have not been elucidated for prostate cancer, several mechanisms have been implicated including environmental factors, age, and genetic factors (1). Treatment for the disease includes cytokine treatment, inhibitor molecules, chemotherapy, radiation, and surgery. A plethora of observations indicates that aberrant expression of proteins known as suppressor of cytokine signaling (SOCS) molecules play a major role in a wide variety of human diseases(2). More specifically, recent evidence suggests that suppressor of cytokine signaling proteins, SOCS1 and SOCS3 may modify prostate cancer progression (3, 4). Therefore, SOCS1 and SOCS3 represent a critical checkpoint that could be used to regulate prostate cancer development and progression.

Understanding the role of signal transduction molecules involved in human cancer is of great importance to biologists (2). Much research is directed at identifying particular molecular markers for detection of potential oncological disorders and for developing targeted molecular inhibitors that may prove useful in counteracting the cellular outcomes observed in many carcinomas, including prostate cancer. In an earlier review, the corresponding author examined the utility of

targeting the Janus kinase-Signal transducer and activator of transcription (JAK-STAT) pathway to ameliorate human cancer development and progression (5). The overall objective of this review is to examine studies that provide key evidence that differential SOCS1 and SOCS3 expression may affect prostate cancer invasion, metastasis, and proliferation and thus serve as beneficial chemotherapeutic targets.

Suppressor of Cytokine Signaling (SOCS) Proteins

SOCS proteins were discovered over twenty years ago and shown to exert negative regulatory effects following cytokine, growth factor, and hormonal stimulation (6-9). The SOCS protein family consists of eight members, SOCS1-SOCS7 and CIS (cytokine-inducible Src homology 2 domain-containing protein). SOCS proteins suppress signal transduction activity in a variety of ways and primarily attenuate the JAK-STAT pathway and other biochemical circuits such as the mitogen-activated protein kinase (MAPK) signaling pathway (7). SOCS proteins modulate many intracellular processes. Research shows that SOCS proteins inhibit signaling pathways induced by interleukins (e.g., IL-2, IL-3, IL-4, IL-6), interferons (e.g., IFNα, IFNγ), hormones (e.g., growth hormone), and colony-stimulating factors (e.g., G-CSF, GM-CSF, erythropoietin) (Table 1).

There are excellent reviews that explore SOCS function in living systems. Previous reviews detail the role of SOCS proteins in cell growth, metastasis, cell differentiation, microbial immune evasion, inflammatory responses, cancer development, and many other biological functions and human diseases including systemic lupus erythematosus, neurodegenerative diseases, and rheumatoid arthritis (2, 10-13). While other members of the SOCS protein family have been implicated as prospective targets for human carcinomas (14, 15), compelling data for SOCS1 and SOCS3 are by far more abundant in the literature.

Table 1: SOCS Proteins and Signaling Molecules

SOCS Proteins	Signaling Molecules	References
CIS	IL-2, IL-3, IL-4, IL-6, IL-10, growth hormone, prolactin, leptin	7, 8
SOCS1	IFNγ, IL-2, IL-4, IL-6, IL-9, G-CSF, GM-CSF, EPO	7, 16
SOCS2	IL-3, IL-4, IL-6, IFNα, LIF, CNTF, growth hormone	7, 8
SOCS3	IL-1, IL-2, IL-3, IL-6, IFNα, LIF, leptin, G-CSF	16, 17
SOCS4	LIF	4, 16
SOCS5	IL-4, IL-6, EGF	7, 8
SOCS6	Insulin, stem cell factor	4, 16
SOCS7	Insulin, growth hormone	4, 17

Structural similarities and differences between SOCS1 and SOCS3 proteins are illustrated in Figure 1. On average, SOCS3 proteins contain approximately 10-20 more

amino acids than SOCS1 proteins and are therefore slightly larger than SOCS1 proteins. Both protein molecules contain an amino-terminal domain, a centrally located Src Homology 2 (SH2) domain, kinase inhibitory region (KIR), and a SOCS box. SH2 domains allow SOCS proteins to bind to phosphorylated tyrosine residues on target proteins, namely JAK proteins and specific receptors.A region adjacent to the SH2 domain contains a conserved amino acid sequence called the extended SH2 domain (ESS) which enhances binding to phosphorylated amino acids. The KIR is located near the amino-terminal end of SOCS1 and SOCS3 proteins and is responsible for suppressing the catalytic activity of JAK molecules. A KIR region has not been identified in other SOCS proteins. Functional similarities of SOCS1 and SOCS3 are attributed to the presence of the KIR domain. The SOCS box is a 40-amino acid region located at the carboxy-terminus and plays a vital role in the recruitment of the ubiquitin-transferase system which facilitates intracellular protein degradation (16, 17). Although different mechanisms of JAK inactivation exist, both SOCS1 and SOCS3 binding complexes subsequently undergo ubiquitination and are targeted for destruction via the proteasome.

SOCS1

SOCS1-deficient mice have been historically utilized to characterize the endogenous physiological functions of SOCS1 (7). It is widely known that $SOCS1^{-/-}$ mice die during neonatal development due to lymphopenia and systemic organ failure resulting from unrestricted IFNγ signaling. Reports indicate that SOCS1 preferentially binds to JAK moleculesand employs the KIR domain to block access of JAK substrates (7). Data published at the turn of the century suggested that an IL-6-activated, STAT3-dependent mechanism induced gene expression that supported tumor development and progression in the prostate cancer cell line, LNCaP(18). Additionally, data by Flowers *et al*. (19, 20) demonstrated that a SOCS1 mimetic peptide could be used to bind to the JAK2 autophosphorylation site and extirpate constitutive and IL-6 induced activation of STAT3in DU145 and LNCaP prostate cancer cell lines, and thereby block mitotic progression and cell proliferation via a cyclin D1-dependent mechanism. Later, in a subsequent study, by Neuwirt *et al*. (21) it was shown that SOCS1 expression produced a cyclin-dependent reduction in cell proliferation in PC3, DU-145, and LNCaP cell lines. Treatment with small interfering RNA molecules targeting SOCS1 in the

prostate cancer cell lines produced an increase in cell growth (21).Recently, an over expression system was used to clarify the role of SOCS1 in prostate cells. Cells expressing SOCS1 showed attenuated cell growth, reduced migration, and suppression of collagen matrix invasion compared to control cells (22). Moreover, using the human tumor xenograft model, SOCS1 expression in tumor cells was studied *in vivo*. Tumor expansion was severely limited in SOCS1-expressing prostate cancer cells in severely compromised immunodeficient (SCID) mice (22).

Chevrier *et al*. (23) used immunohistochemical staining experiments to demonstrate that SOCS1 protein expression may be used to evaluate prostate cancer progression in cancer patients. Results from their experiments showed that SOCS1 staining in prostatectomy samples was inversely correlated with disease progression, suggesting that identification of SOCS1 may be a useful prognostic indicator. Moreover, a study using human prostate tissues showed that STAT proteins and SOCS1 proteins are upregulated in prostate cancer cases compared to BPH controls. Results of the study provide additional evidence that SOCS1 is potentially important in modifying signaling pathways and inhibiting tumorigenic transformation mechanisms (24). Collectively, these results demonstrate that SOCS1 can exert an antitumor effect on prostate cancer cell lines and human prostate tissues by downregulating various signaling proteins that promote tumor development, progression, and metastasis.

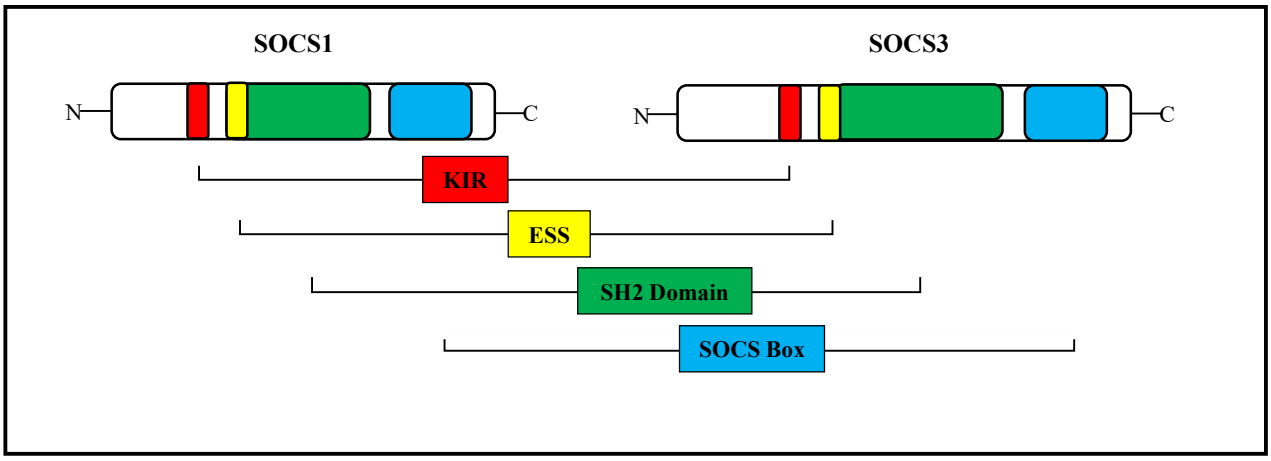

Figure 1: Major Structural Elements of SOCS1 and SOCS3 Proteins

SOCS3

SOCS3 knockout mice have generated a copious amount of data regarding the intracellular functions of SOCS3 (8). In contrast to SOCS1, $SOCS3^{-/-}$ mice demonstrate a prenatal lethality due to abnormal placenta development (7). Further, studies by Croker et al. (25) showed that SOCS3 negatively regulates IL-6 and G-CSF in hematopoieticcells in a STAT3-dependent manner. It is widely accepted that SOCS3 binds to JAK-associated receptors, not JAK directly, and employs the KIR domain to serve as a pseudosubstrate in the JAK activation loop to obfuscate downstream effector responses mediated by JAK activation. Resveratrol is a phytoalexin that has been shown to exert some antitumor properties by inducing apoptosis in prostate cancer cells (26).Horndasch and Culig (27) demonstrated that SOCS3 blocks proapoptotic effects of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and resveratrol in prostate cancer cell lines. It was determined using immunoprecipitation assays that SOCS3 mediates antiapoptotic effects in cancer cells by binding to cell death receptors (27).

Investigators also demonstrated that SOCS3 expression negatively affects cellular proliferation and metastasis following fibroblast growth factor2 (FGF-2) stimulation of prostate cells. In this study, prostate cancer cell lines were treated with FGF-2 and western blot analysis was used to ascertain phosphorylation of STAT3, STAT1, and MAPK proteins. Only p44/p42 MAPK pathway proteins were phosphorylated, and phosphorylation was abolished due to SOCS3 interference (28). Other investigators demonstrated that both ZFP36 and SOCS3 expression are associated with lower Gleason scores and decreased metastatic potential of prostate tissues(29). Examination of SOCS3 protein expression using microscopic methods provide a potentially useful approach to assess the nature of prostate carcinomas and suggests that SOCS3 may be a beneficial biomarker. Additionally, scoparone, an organic compound extracted from *Artemisia capillaris,* exerted antitumor effects on DU145 prostate cancer cells by downregulating STAT3 and SOCS3(30). These results provide more evidence that SOCS3 plays an important role in prostate cancer progression and development.

CONCLUSIONS

Recent data is a harbinger of the potential therapeutic benefits of targeting SOCS1 and SOCS3 in the treatment of prostate cancer. The synergy of microarray studies and

bioinformatics analysis will positively affect research investigations into the underlying molecular mechanisms of prostate cancer. Therapies that enhance or minimize SOCS1/SOCS3 expression could be efficacious in preventing the development and progression of prostate cancer.

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