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Review Article

A review on the Dual Role of SOCS3 in Cancer

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Abstract

Background: Aberrant proliferation is a hallmark of cancer. Cellular proliferation mechanisms and various cytokines contribute to the progression of cancer. The tumor suppressor protein Suppressor of Cytokine Signalling 3 (SOCS3), which acts via the JAK/STAT pathway, have a role in the progression of cancer.
Aim: To explore the role of SOCS3 in all the hallmarks of cancer. To exhibit SOCS3 action on proliferation pathways and immune aspect affecting cancer progression.
Methods: The PubMed database was searched using the keywords proliferation, SOCS3, JAK/STAT, interleukins, and tumor suppressor. Articles relevant to SOCS3 were considered for this review.
Results: In this review, we have illustrated the dual action of SOCS3, which inhibits various proliferative mechanisms and affects certain interleukins that counterbalance the progression of cancer. In addition, SOCS3 affects all the hallmarks of cancer.
Conclusion: We hope that this review will stimulate further investigation of SOCS3, which has the potential to become a new target for the pharmacological treatment of various cancers in the future.

Keywords: Cancer, SOCS3, JAK/STAT, Interleukins, Proliferation

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Introduction

Neoplasms result from aberrant uncontrolled growth of tissues in the body due to external or internal stimuli [1]. Emerging hallmarks and enabling characteristics of cancer include the dysregulation of cellular energetics, immune evasion, genomic instability and mutation, and inflammatory mediators' promotion of cancer growth [2]. Cancer growth is enhanced by tumour promoter proteins such as TNFα [3] and indoleamine 2,3 dioxygenase (IDO) [4]. On the other hand, tumor suppressor proteins, including p53 [5], Rb [6], and SOCS3 [7] counterbalance cancer growth. Tumor suppressors have a profound action on cell cycle progression [1]. Loss of tumour suppressor proteins has been demonstrated to result in the progression of precancerous conditions to cancer [1]. Several tumor suppressor genes and proteins have been discovered, such as Rb (cell cycle regulator) [6], p53 (cell cycle and apoptosis regulator) [5], WT1 (transcriptional regulation) [8], NF1 (Ras inactivation) [9], APC (signalling through adhesion molecules to the nucleus) [10], MEN1 (DNA repair) [11], VHL (activation of the ubiquitin complex) [12], MSH2 / MHL1 (DNA mismatch repair) [13], TSC1 / TSC2 (mTOR inhibitor) [14], DPC 4/SMAD4 (TGFβ/BMP signalling regulator) [15], BRCA1/BRCA2 (DNA repair/chromosomal stability) [16] and the new tumour suppressor gene SOCS3 (inhibits the JAK/STAT pathway [17]; upregulates cytotoxic T cells [18]), which are all involved in cancer progression.

Method of data collection

To explore the role of SOCS3 in cancer proliferation, the publicly available PubMed search engine was used with keywords proliferation, SOCS3, JAK/STAT, interleukins, and tumor suppressor. Articles relevant to SOCS3 with >2

citations in PubMed and published in a journal with an impact factor >1 were considered for this review.

SOCS3

Cytokines largely control homeostasis of the hematopoietic and immune systems [19]. The cytokine initiates JAK (Janus kinases) which is intracellular signalling of receptor bound tyrosine kinases that activates transcription factors STAT (signal transducer and transcription activator) that results in appropriate biological responses [19]. Although to avoid prolonged activation of JAK/STAT pathway that may result in aberrant proliferation of cells, the JAK/STAT pathway is tightly regulated by SOCS (suppressor of cytokine signalling) regulator proteins [20]. The SOCS family consists of eight different types of proteins. One of them is SOCS3 [20].

SOCS3 in cancer cases

SOCS3 has been found to be involved in the progression of various human cancers. Decreases in the level of SOCS3 have been seen in liver [21] and breast cancer [22], and methylation of the promoter sequence of SOCS3 has been linked to prostate [23], head and neck [24], lung [25], oesophageal [26], colorectal [27], ovarian [28], and brain cancer [29]. SOCS3 is involved in various mechanisms that contribute to cancer progression (Table 1). Furthermore, SOCS3 affects tumor immune evasion by regulating various cytokines that play an important role in immune-mediated cancer progression/destruction and other aspects of cancer growth.

SOCS3 and cancer proliferation

Cancer proliferation involves various mechanisms, such as the Wnt [44], PI3K/Akt [45], Ras/MAPK [46], JAK/STAT [47], TGFβ/Smad3/4 [48], and mTOR signalling pathways [49]. These pathways are well known and interact via crosstalk with each other, promoting cancer progression [50]. All these pathways can be inhibited by tumour suppressor proteins [51].

SOCS3, considered to be a tumour suppressor protein, primarily acts on the JAK/STAT pathway [17]. STAT3, an oncogene [52], regulates proteins including bcl-2, bcl-xl, mcl-1, and Fas [53], and upregulates cyclin D1, cyclin E1, and p21 [54]. STAT3 autophosphorylates tyrosine 757 (mouse) and 759 (human) within the gp130 SH2 domain, activating various proliferative signals [55]. TGFβ and Smad3/4 (part of the bone morphogenetic protein family) interact, resulting in TGFβ target genes being inhibited by SOCS3 (pathway 1, Figure 1) [55]. SOCS3 inhibits IDO and therefore inhibits the Wnt pathway (pathway 2, Figure 1) [56]. Ras (serine/threonine protein kinase) activates RAF, MEK (serine/tyrosine/threonine kinase) and ERK (extracellular receptor kinase), leading to proliferation, which is inhibited by SOCS3 (pathway 3, Figure 1) [57]. PI3K (phosphoinositide 3-kinase) transforms PIP2 (phosphatidylinositol (3,4) bisphosphate) to PIP3 (phosphatidylinositol (3,4,5) trisphosphate), leading to the activation of Akt (protein kinase B) and proliferation, which is inhibited by SOCS3 (pathway 4, Figure 1) [30]. Akt enables the TSC1 and TSC2 tuberous sclerosis 1 and 2 complex interaction that activates Rheb (Ras homologue-enriched in brain), leading to mTOR (mammalian target of rapamycin) activation of S6K (ribosomal 40S subunit substrate 6 kinase protein) and ultimately proliferation. This pathway is also inhibited by SOCS3 (pathway 5, Figure 1) [30].

SOCS3 and immune regulation

A plethora of information is available from previous studies to indicate the potential role of the immune system in combating the growth of cancer. NK cells produce interleukins, C-X-C motif chemokines (CXCLs), which inhibit cancer progression [58]. IL-6 has both pro-inflammatory and anti-inflammatory actions [59]. Plasma levels of IL-6 vary under different physiological conditions; for example, during exercise, in obesity, and in sepsis [60]. The IL-6/IL-6R complex binds to gp130, which activates the JAK/STAT pathway [61]. Activated STAT induces SOCS3, which inhibits various cytokines, including IL-6, IL-10, and interferon γ [62]. Therefore, SOCS3 exerts negative feedback control over the JAK/STAT pathway and downregulates IL-6 [62]. Previous studies have found that ulcerative colitis-induced colon cancer is directly affected by the IL6/TNFα/STAT3 complex, which influences Treg cells to aid in the evasion of immune-mediated destruction and thus the progression of cancer [63]. SOCS3 has been shown to inhibit this complex and downregulate Treg cells [63]. On the other hand, the IL-6/STAT3 complex mediates transcriptional repression of SOCS3, which promotes pancreatic cancer growth and metastasis [64].

Table 1: SOCS3 affecting different hallmarks of cancer

Aspect of cancer	Mechanisms	Role of SOCS3	References
Sustaining proliferative signals	Ras, myc; B-Raf; MAPK; PI3K/Akt/PKB; Loss of function of PTEN	SOCS3 binds to STAT3, thus inhibiting the activation of proliferative mechanisms	[2], [30]
Evading growth suppressors	Loss of function of TP53 and RB; defects in NF2 gene product; defects in LKB1, mechanism of contact inhibition; aberrant behaviour of TGFβ	SOCS3 overexpression can arrest the growth of tumours in p53 and PTEN deficient xenografts	[2], [31]
Inhibiting cell death	Autophagy; necrosis	Autophagy regulates SOCS3; IL-6 inhibits apoptosis in pancreatic cancer by stimulating autophagy	[2], [32], [33]
Enabling replicative immortality	Telomere, TERT, break-fusion-bridge cycles	IL6/STAT3/SOCS3 affects senescence associated secretory phenotype	[2], [34], [35]
Inducing angiogenesis	VEGF, TSP-1, FGF	SOCS3 inhibits HIF-1α to inhibit proliferation and angiogenesis	[2], [36]
Invasion and metastasis	EMT and MET; reduction of E-cadherin, Snail, Slug, Twist, and Zeb1/2; CCL5 and RANTES	Suppression of SOCS3 in macrophages prevent metastasis in melanoma; SOCS3 suppresses MMP-13 transcriptional activity; overexpression of SOCS3 reduces metastasis in colorectal cancer	[2], [37], [38]
Tumour-promoting inflammation	Chemokines, cytokines, prostaglandins	SOCS3 negatively regulate interleukins that help in tumour-promoting inflammation (see Table 2)	[2], [39], [40]
Genome instability and mutation	Comparative genomic hybridisation revealed the loss and gain of gene copy numbers across the genome	SOCS3 inhibits PI3K activation; PI3K mutation is often seen in genomic instability	[2], [41], [42]
Dysregulation of cellular energetics	Glycolysis and anaerobic glycolysis by upregulating GLUT 1	SOCS3 binds to pyruvate kinase type M2 in dendritic cells (DC) and reduces ATP production in cancer cells	[2], [36], [43]
Avoiding immune destruction	CD8+ cytotoxic T lymphocytes (CTLs), CD4+Th1 helper T cells or natural killer (NK) cells decrease; upregulation of T_{reg}; binding of T_{reg} to APC leading to T-cell anergy and death	SOCS3 upregulates T-helper cells ($T_{effector}$)	[2], [18]

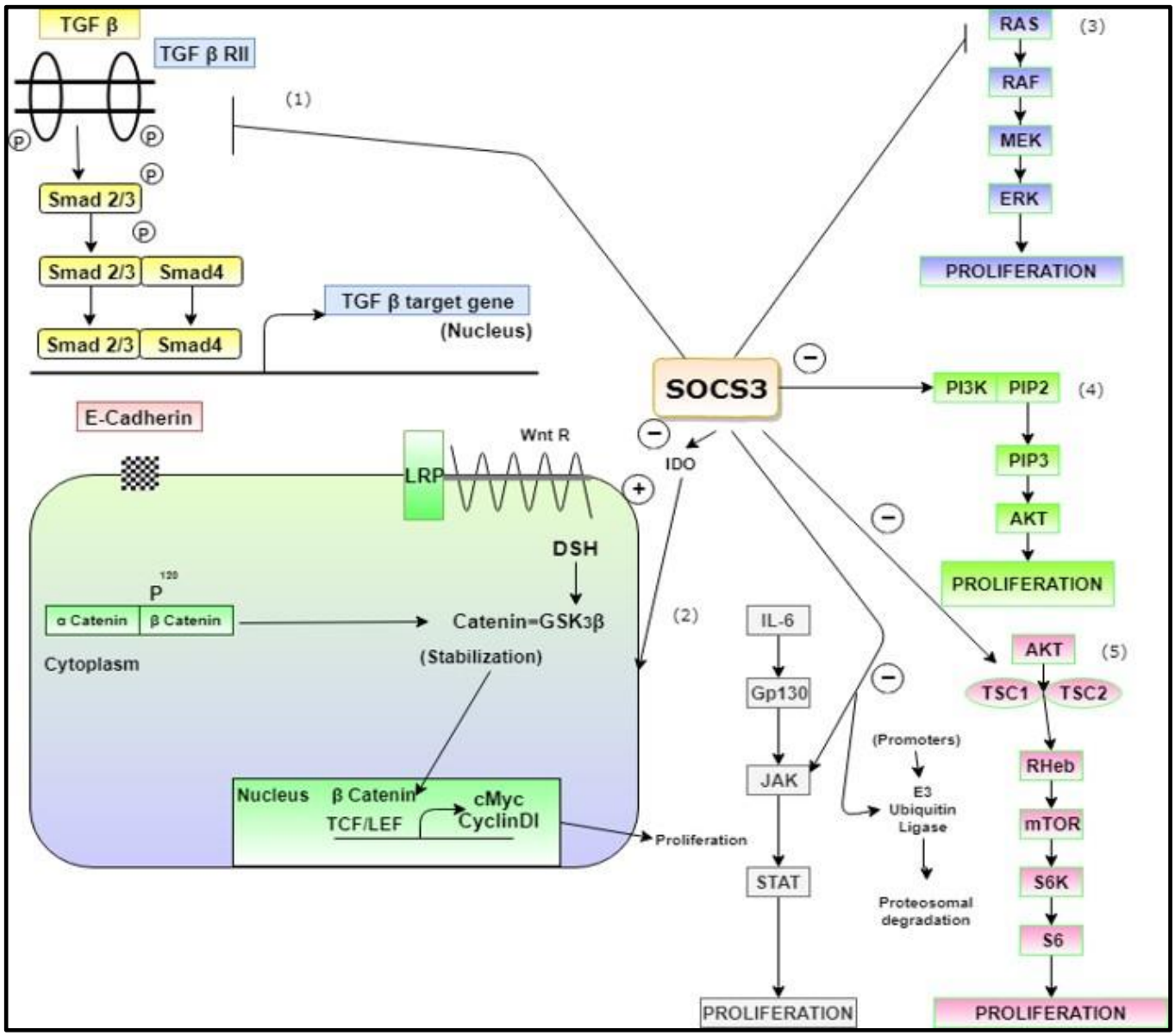

Figure 1: SOCS3 regulation of cancer cell proliferative mechanisms. SOCS3 affects various cancer proliferation pathways like TGF β, Ras/MAPK, mTOR, JAK/STAT, and Wnt pathways

IL-6 has frequently been observed to act in cancer initiation and progression. IL-6-mediated activation of STAT3 drives cancer progression by facilitating the transcription of target genes such as cyclin D1, c-myc, JunB, c-fos, C/EBPβ and C/EBPδ and mTORC1 [65]. STAT3 also facilitates the expression of c-myc, which increases proliferation in cancer cells by affecting the transition from G1 to S phase by inactivating repressor complexes like E2F [65]. Furthermore, the STAT3/IL6 complex induces anti-apoptotic proteins such as bcl-2, bcl-xl, and survivin and suppresses p53 [65]. IL6/STAT3 also has been shown to increase angiogenesis by inducing vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF), as well as metastasis, by upregulating matrix metalloproteinases (MMPs) [65]. IL-6 phosphorylates gp130 (glycoprotein 130), which leads to autophosphorylation of serine 757 in the STAT3 domain, activating the JAK/STAT pathway and promoting proliferation. This pathway is also inhibited by SOCS3, which can also promote proteasomal degradation of the E3 ubiquitin ligase (pathway 6, Figure 1) [17]. Apart from IL-6, SOCS3 also affects various other interleukins.

SOCS3 and Treg cells

Sakaguchi et al. first identified a population of regulatory T cells (Treg) in CD4+ T-cells expressing

high levels of CD 25 that exhibited escape from autoimmunity in a mouse model [66]. The transcription factor for Treg cells is FOXP3 [66]. Thus, CD4+CD25highFOXP3+Treg produces T-cell anergy by inhibiting CD4+CD25- T-cells, CD8+ T-cells, DCs, NK cells, NK T-cells and B cells [66]. Immunohistochemical analysis showed co-expression of FOXP3+Treg cells and CD11c DC+, FOXP3-CD4+T-cells, and CD4+T-cells in T-cell regions of lymph nodes, suggesting a definitive role of Treg cells in the progression of cancer [66]. Furthermore, COX2 / PGE2 overexpression in a mouse lung cancer model showed upregulation of Treg and FOXP3 expression [66]. Treg have also been shown to be upregulated in cases of breast, cervical, pancreatic, head and neck, ovary and colorectal cancer [67].

SOCS3 regulates the activation and differentiation of CD4 + T cells, preferentially promoting Th1 and Th2 differentiation [18, 68]. The deletion of SOCS3 from T cells results in suppression of both Th1 and Th2 differentiation [68]. The deletion of SOCS3 in T lymphocytes results in upregulation of CTLA4 and expansion of Treg cells [68]. Treg cells reduce Teffector cells [69], thus contributing to tumour escape of immune-mediated destruction [2]. SOCS3 overexpression leads to deficient FOXP3+ expression of FOXP3 + and Treg cell level via the SOCS3/IL-2 axis [18]. SOCS3 has also been shown to upregulate T-helper cells and regulate proliferation [18]. SOCS3 upregulates IL-6, which lowers Treg (pathway 1, Figure 2) [37]. TGFβ and IL-23 promote Th 17 differentiation. Th 17 is responsible for angiogenesis. SOCS3 inhibits TGFβ/IL-23, which inhibits IL-17 (pathway 2, Figure 2) [39]. IL-10/TGFβ promotes the binding of CTLA4 to B7 and the CD80/86 receptor site of DCs (APC), resulting in T-cell anergy/death (pathway 3, Figure 2) [70]. SOCS3 inhibits IL-10/TGFβ-mediated CTLA4 binding to APC (pathway 4, Figure 2) [70]. SOCS3 facilitates CD28 (Teffector) binding to APC with the help of IL-2, IFNγ and IL-4 (pathway 5, Figure 2) [37]. SOCS3 inhibits TGFβ, resulting in upregulation of Teffector cells and downregulation of Treg cells (pathway 6, Figure 2) [70]. IL-10 induces SOCS3 (pathway 7, Figure 2) [71].

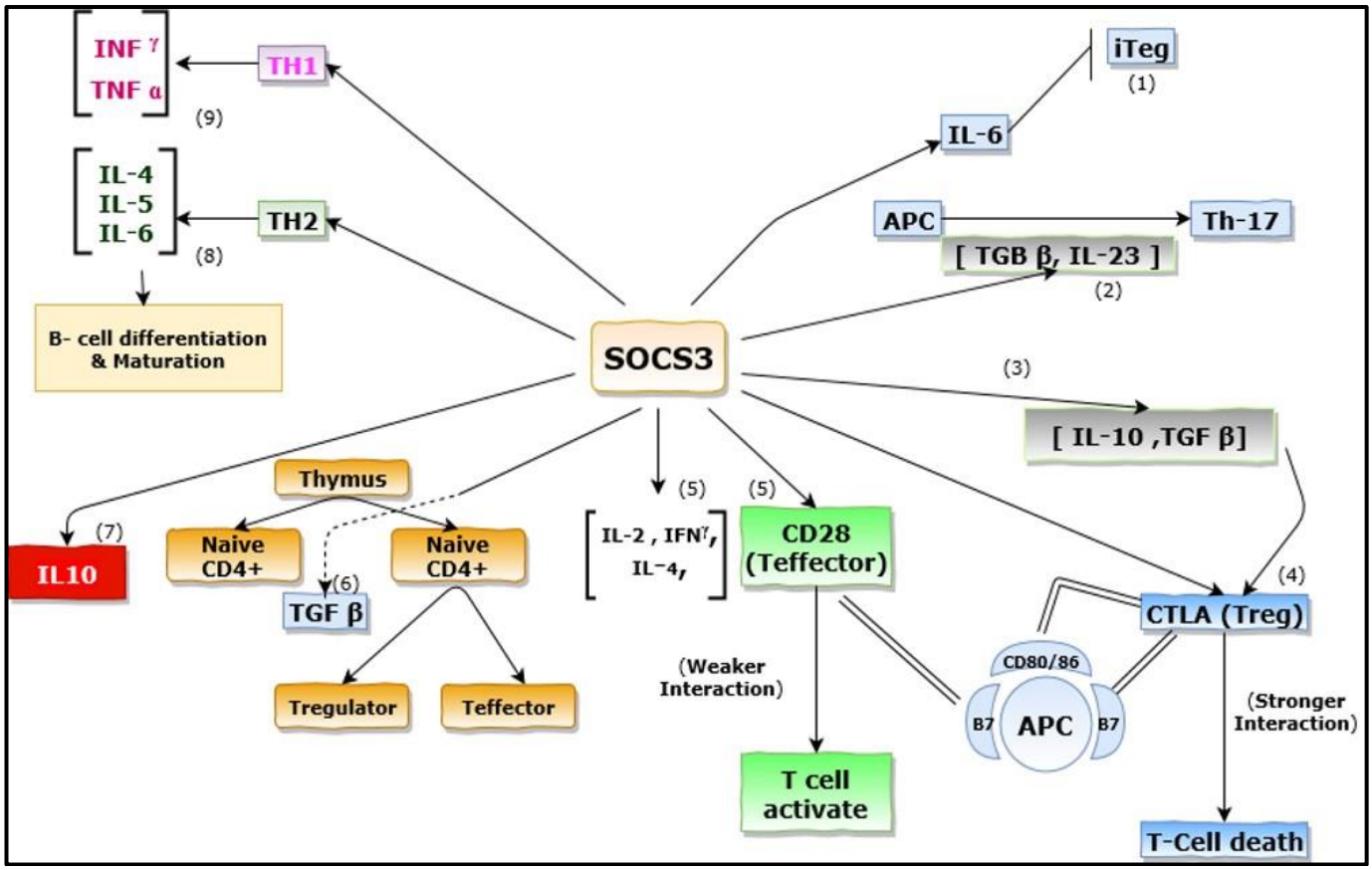

Figure 2. SOCS3 regulation of various cytokines. SOCS3 affecting various interleukins resulted in proliferation of cancer cells by escaping immune attack

SOCS3 promotes Th2 differentiation, resulting in B-cell differentiation and maturation (pathway 8, Figure 2) [70]. SOCS 3inhibits Th 1 differentiation by inhibiting IL-12, which results in inhibition of IFNγ and TNFα (pathway 9, Figure 2) [72]. Thus, suggesting that SOCS3 has potential role in the development of Treg and Teffector cells in cancer. More experiments are required to elucidate the role of SOCS3 in immune evasion.

Other effects

Indoleamine 2,3-dioxygenase (IDO) is the first rate limiting enzyme of the kynurenine pathway [73]. IDO has been noted to upregulate Treg cells and thus enable cancer to escape immune-mediated destruction [4]. IDO has been also reported to contribute to the stabilisation of various cancer proliferative mechanisms [4], and overexpression of IDO has been found to be related to poor prognosis in various cancers [73]. SOCS3 has been found to contribute to the proteasomal degradation of IDO [73]. IDO inhibits GSK3β, which is activated by DSH (dishevelled cytoplasmic phosphoprotein). LRP (Low-density lipoprotein-related protein) inhibits β catenin, which is activated by interacting with α catenin after activation of E-cadherin (responsible for cell-cell interaction). This enables β catenin translocation to the nucleus, where it activates TCF (T-cell factor) and LEF (lymphoid enhancer factor), activating the transcription of cyclin D1, c-myc and other matrix metalloproteinase genes responsible for cancer proliferation and metastasis. Recently we found SOCS3 also has a role in bacterial antigen induced proliferation of oral cancer cells [74, 75].

Conclusions

SOCS3 is a tumor suppressor protein. Much research has identified its potent role in the inhibition of progression in various types of cancer. However, to date, there has been no research into SOCS3 in clinical trials. In the future, SOCS3 overexpression or deletion could be attempted in different types of cancer cells, and the effect on their proliferation, differentiation, and apoptosis could be assessed using various biochemical and cell biological techniques. The pathways related to proliferation and apoptosis must also be determined. Cancers such as oral squamous cell carcinoma and colorectal cancer may have cofounders, such as various commensal or biofilm-related bacteria. In future, therefore, the interaction of microbial organisms and SOCS3-cancer cells might be harnessed. These microbial populations can be characterised through the mass spectrometric (MS) analysis of the corresponding cancerous tissues in which corresponding proteins are detected via Trans-Proteomic pipeline. Liquid chromatography-mass spectrometry analysis (LC-MS) allows the characterisation of the metaproteomic profile of cancer cells, which helps in the investigation of protein-protein interaction of SOCS3 and microbial proteins. In the future, research could be undertaken to create SOCS3 mimicking agents that can block the progression of cancer. Therefore, we propose to synthesise newer pharmacological agents that can mimic SOCS3 activities and thereby inhibit cancer growth of cancer and thus improve the toxic effects of chemotherapy in the treatment of cancer.

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Authors' contribution

Conception or design: RC; Acquisition, analysis or interpretation of data: RC; Drafting or revising the manuscript: RC, CD, AAAA, HH, KV; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Not applicable.

Ethical considerations

Not applicable.

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Study registration

None.

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