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RESEARCH ARTICLE

PROGNOSTIC SIGNIFICANCE OF SOCS IN REGULATING CANCER PROGRESSION

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Abstract

Suppressor of cytokine signalling (SOCS) proteins have emerged as crucial regulators in cancer progression, exhibiting significant prognostic implications. This review explores the prognostic significance of SOCS in various cancer types and their role in modulating key signalling pathways involved in tumour growth, metastasis, and immune evasion. Understanding the intricate interplay between SOCS proteins and cancer progression provides valuable insights into developing targeted therapies and prognostic markers for improved patient management and outcomes. SOCS proteins are pivotal regulators of immune responses and inflammation, but their dysregulation has been implicated in cancer development and progression. We explore the mechanisms by which SOCS proteins exert their effects on oncogenic signalling pathways, such as JAK/STAT, PI3K/AKT, and MAPK pathways, highlighting their potential as therapeutic targets. Furthermore, understanding the complex interplay between SOCS proteins and cancer holds promise for the development of novel therapeutic strategies and precision medicine approaches tailored to individual patients.

Introduction:-

SOCS proteins are crucial regulators of cytokine signalling pathways, playing pivotal roles in modulating immune responses, inflammation, and cellular homeostasis [1]. The SOCS protein family consists of eight members: SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6, SOCS7, and cytokine-inducible SH2-containing protein (CIS). These proteins are characterized by a central Src homology 2 (SH2) domain and a conserved C-terminal SOCS box motif [2]. Overall, SOCS proteins serve as key regulators of cytokine signalling and immune responses, with broad implications for various physiological and pathological processes, including cancer [3]. Understanding the intricate mechanisms underlying SOCS protein function is essential for elucidating their roles in health and disease and for developing novel therapeutic strategies targeting these proteins [4].SOCS proteins are integral components of the immune regulatory network, playing critical roles in fine-tuning immune responses and maintaining immune homeostasis. Dysregulation of SOCS proteins can have profound implications for immune function and

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inflammatory diseases, highlighting their importance as potential therapeutic targets for immune-mediated disorders [5].

Dysregulated SOCS proteins and cancer development

SOCS proteins have emerged as significant contributors to cancer development. Aberrant expression or function of SOCS proteins disrupts the delicate balance of cytokine signalling pathways, leading to uncontrolled cellular proliferation, survival, and evasion of immune surveillance [6]. SOCS proteins, such as SOCS1 and SOCS3, act as tumour suppressors by inhibiting oncogenic signalling pathways like JAK/STAT and PI3K/AKT, thus restraining tumour growth [7]. Conversely, downregulation or inactivation of SOCS proteins promotes tumour progression by facilitating tumour cell proliferation, invasion, and metastasis [8]. Additionally, dysregulated SOCS proteins contribute to immune evasion mechanisms employed by cancer cells, fostering a tumour-permissive microenvironment [9]. Understanding the intricate interplay between dysregulated SOCS proteins and cancer development provides valuable insights for the identification of novel therapeutic targets and the development of precision cancer therapies [10].

Structure and Function of SOCS Proteins

Functionally, SOCS proteins act as negative feedback regulators of cytokine signalling pathways. Upon cytokine stimulation, SOCS proteins are induced and act to inhibit signalling cascades by multiple mechanisms [11]. Inhibition of Janus Kinases (JAKs): SOCS proteins bind to JAK kinases via their SH2 domain, blocking their activation and subsequent phosphorylation of downstream targets [12]. Target Protein Degradation: SOCS proteins recruit target proteins, such as cytokine receptors and signalling intermediates, to E3 ubiquitin ligase complexes through their SOCS box motif, leading to ubiquitination and degradation via the proteasome pathway [13]. Competition for Binding Sites: SOCS proteins can compete with signalling molecules, such as STAT proteins, for binding to cytokine receptors or other regulatory proteins, thereby preventing their activation and downstream signalling [14]. Regulation of Signalling Complex Assembly: SOCS proteins can interfere with the formation of signalling complexes by disrupting protein-protein interactions necessary for signal transduction [15].

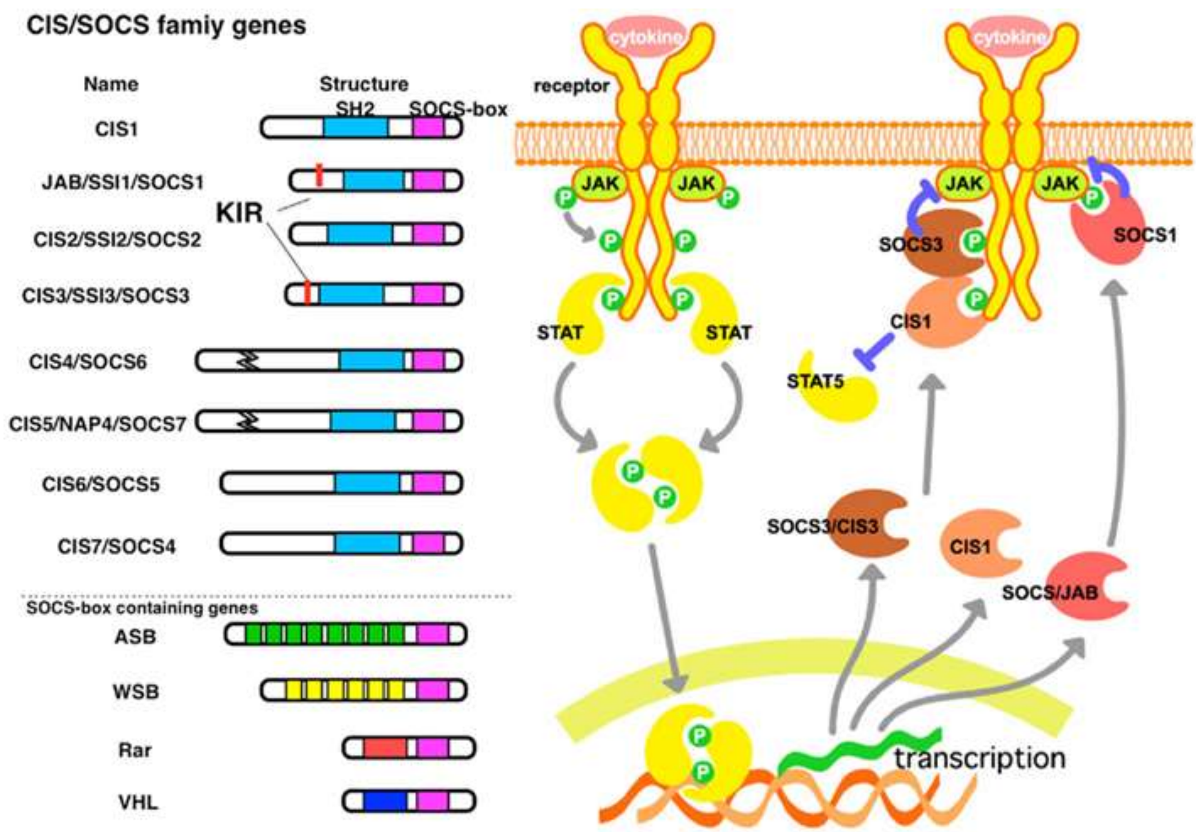

Figure 1:- SOCS proteins inhibit signalling cascades by multiple mechanisms, image courtesy Yoshimura A et. al., [16].

Role of SOCS Proteins in Cancer Initiation and Progression

SOCS proteins play dual roles in cancer initiation and progression, acting as both tumour suppressors and oncogenes depending on the context of specific signalling pathways and cellular environments [17]. Initially identified as negative regulators of cytokine signalling, SOCS proteins such as SOCS1 and SOCS3 inhibit the activation of Janus kinases (JAKs) and subsequent downstream signalling events, thereby restraining cellular proliferation and survival. Consequently, loss of function or reduced expression of SOCS proteins can unleash aberrant cytokine signalling, promoting tumour initiation and growth [18]. Paradoxically, in certain contexts, SOCS proteins can also facilitate tumour progression by modulating signalling pathways involved in epithelial-mesenchymal transition (EMT), metastasis, and immune evasion [19]. For instance, SOCS1 and SOCS3 have been implicated in promoting tumour invasion and metastasis through interactions with components of the extracellular matrix and regulation of cell adhesion molecules. Moreover, SOCS proteins can exert immunosuppressive effects by inhibiting cytokine-mediated immune responses, thus creating an immunosuppressive tumour microenvironment conducive to tumour growth and immune evasion [20]. Overall, the role of SOCS proteins in cancer initiation and progression is complex and context-dependent, highlighting their potential as both therapeutic targets and prognostic markers in cancer management [21].

SOCS expression patterns in different cancer types

SOCS proteins exhibit diverse expression patterns across various cancer types, reflecting their multifaceted roles in tumour development, progression, and immune evasion [22]. Understanding these expression patterns is crucial for elucidating the specific contributions of SOCS proteins to different cancer phenotypes and for identifying potential prognostic markers and therapeutic targets [23]. In many solid tumours, including breast, colorectal, lung, and prostate cancers, reduced expression of SOCS proteins, particularly SOCS1 and SOCS3, is frequently observed [24]. This downregulation is often associated with poor clinical outcomes, increased tumour aggressiveness, and resistance to therapy. For example, in breast cancer, decreased SOCS1 expression correlates with enhanced tumour growth and metastasis, while in colorectal cancer, low levels of SOCS3 are associated with tumour invasion and poor prognosis. Conversely, elevated expression of certain SOCS proteins, such as SOCS2 and SOCS3, has been reported in hematological malignancies like leukemia and lymphoma [25].

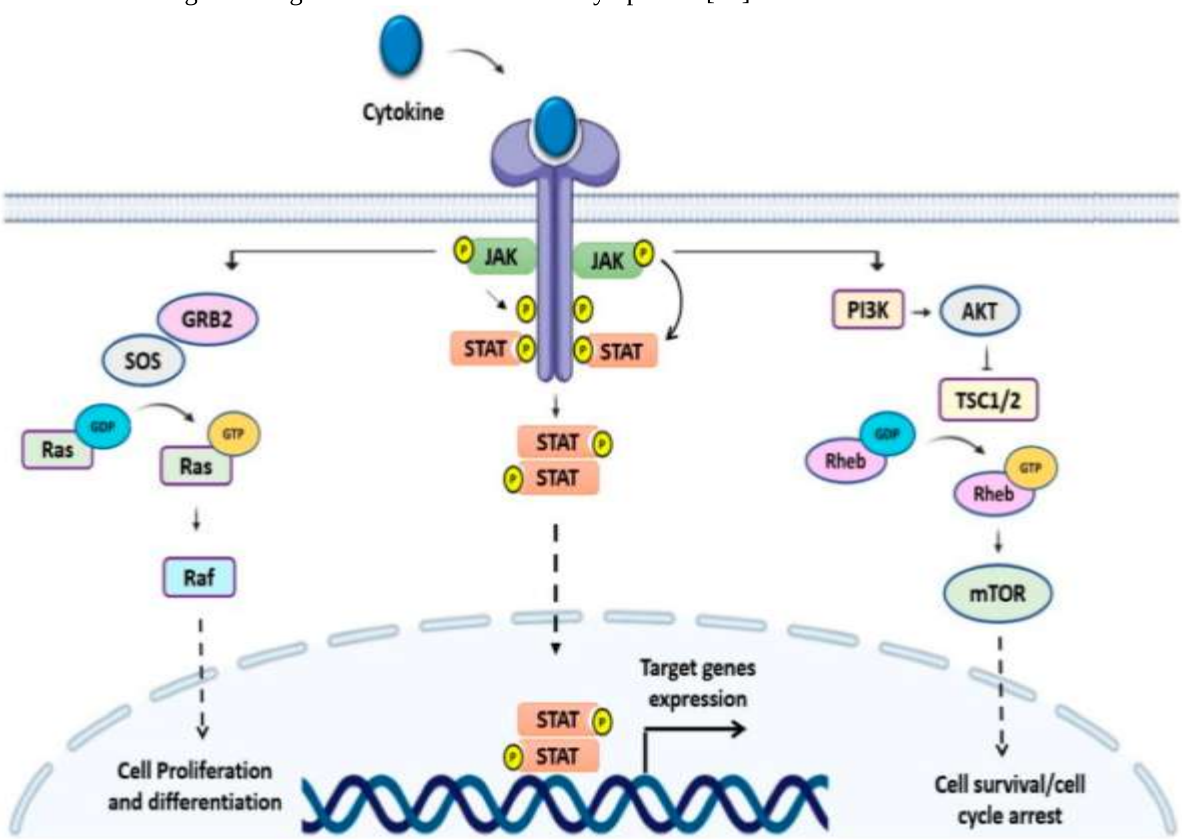

Figure 2:- SOCS expression patterns in different cancer types, image adapted fromKeewan E et. al., [25].

In these contexts, increased SOCS expression may contribute to tumour cell survival and chemoresistance by inhibiting apoptosis and promoting cell proliferation [26]. Furthermore, the expression patterns of SOCS proteins can vary within specific cancer subtypes or stages. For instance, in hepatocellular carcinoma (HCC), SOCS1 and SOCS3 expression levels may differ between early and advanced stages of the disease, with low SOCS1 expression associated with tumour progression and poor prognosis [27]. Similarly, in melanoma, SOCS1 expression may be downregulated in primary tumours but upregulated in metastatic lesions, suggesting distinct roles for SOCS proteins in different stages of disease progression. The dysregulated expression of SOCS proteins in cancer is often influenced by various factors, including genetic alterations, epigenetic modifications, and microenvironmental cues [28]. Consequently, the expression patterns of SOCS proteins can serve as potential biomarkers for cancer diagnosis, prognosis, and treatment stratification. Moreover, targeting aberrant SOCS expression or function holds promise for the development of novel therapeutic interventions aimed at disrupting oncogenic signalling pathways and enhancing antitumour immune responses [29].

Therapeutic Targeting of SOCS Proteins in Cancer

Therapeutic targeting of Suppressor of Cytokine Signalling (SOCS) proteins represents a promising strategy for cancer treatment, given their pivotal roles in modulating oncogenic signalling pathways and immune responses [30]. Several approaches have been explored to target SOCS proteins, aiming to restore their function as tumour suppressors or inhibit their oncogenic activities, thereby impeding tumour growth and enhancing therapeutic efficacy [31].

Small Molecule Inhibitors:

Designing small molecule inhibitors that disrupt the interaction between SOCS proteins and their binding partners has emerged as a potential therapeutic approach [32]. These inhibitors can target specific domains of SOCS proteins, such as the SH2 domain, preventing their association with upstream signalling molecules or cytokine receptors. By blocking SOCS-mediated inhibition of signalling pathways, these molecules can enhance antitumour immune responses and sensitize cancer cells to conventional therapies [33].

Gene Therapy Strategies:

Gene therapy approaches aimed at restoring or augmenting SOCS expression in cancer cells have been investigated [34]. This includes gene delivery systems, such as viral vectors or nanoparticles, encoding SOCS genes or regulatory elements that enhance endogenous SOCS expression. By reinstating the tumour-suppressive functions of SOCS proteins, these strategies can inhibit oncogenic signalling cascades, promote apoptosis, and suppress tumour growth [35].

Combination Therapies:

Combining SOCS-targeted therapies with conventional cancer treatments, such as chemotherapy, radiation therapy, or immunotherapy, holds potential synergistic benefits [36]. For example, combining SOCS inhibition with immune checkpoint blockade therapy can enhance antitumour immune responses by alleviating immune suppression within the tumour microenvironment. Similarly, combining SOCS inhibition with targeted therapies directed against specific oncogenic signalling pathways can overcome resistance mechanisms and improve treatment outcomes [37].

Future Perspectives and Challenges

Future perspectives of SOCS proteins in cancer entail exploiting their therapeutic potential as targets for precision medicine and immunotherapy [38]. Challenges include deciphering the intricate interplay of SOCS proteins within tumour microenvironments, optimizing delivery systems for targeted therapies, and identifying biomarkers predictive of treatment response. Advancing our understanding of SOCS protein dysregulation in diverse cancer contexts will pave the way for innovative therapeutic interventions and personalized cancer care [39].

Conclusion:-

SOCS proteins play multifaceted roles in cancer, acting as both tumour suppressors and oncogenes, depending on the context of specific signalling pathways. Dysregulation of SOCS proteins contributes to tumour initiation, progression, metastasis, and immune evasion, making them attractive targets for cancer therapy. Key findings underscore the importance of elucidating the complex interactions between SOCS proteins and oncogenic signalling pathways, as well as their impact on the tumour microenvironment and immune responses. Future research should focus on uncovering the molecular mechanisms underlying SOCS protein dysregulation in different cancer types and stages, as well as developing targeted therapies that exploit their therapeutic potential. Incorporating SOCS protein expression profiles into clinical practice may enable personalized treatment strategies and improve patient outcomes in cancer management.

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