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Suppressor of cytokine signaling and rheumatoid arthritis

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Rheumatoid arthritis (RA) is a systemic, chronic, progressive disease of unknown etiology which primarily affects synovial joints and is characterized by deregulated innate and adaptive immunity [1]. In addition to synovial joints, many other peripheral organs may also be affected by RA pathology, most notably, heart [2], eye, skin, lung and kidney.

The function of T-cells in general and T-cell subsets, B-cells, neutrophils, mast cells, macrophages and antigen-presenting dendritic cells as well articular chondrocytes and synovial fibroblasts are all significantly metabolically compromised in RA which has been correlated with defects at the molecular level. In that regard, altered function of these cells can generally be traced back to defective regulation of individual signal transduction pathways, involving primarily the mitogen-activated protein kinase (MAPK) pathway, [3-5] the Janus kinase/Signal Transducers and Activators of Transcription pathway (JAK/STAT) [6-9], the Toll-like receptor pathway [10-12] and the phosphatidylinositol-3-kinase/Akt/ mechanistic target of rapamycin (PI3K/PKB/mTOR) pathway [13-16]. In addition, deregulated signal transduction in the cells from RA joint tissues is also likely to involve "cross-talk" between signaling cascades leading to continuous activation between these various receptor-mediated signaling pathways [4].

A prominent feature of RA which contributes to the constitutive activation of signal transduction pathways occurs as a consequence of up-regulating pro-inflammatory cytokine gene expression, exemplified most prominently by interleukin-1β (IL-1β), IL-2, IL-6, IL-7, IL-12/IL-23, IL-15, IL-17, IL-18, IL-19/20, IL-22, IL-32, tumor necrosis factor-α (TNF-α), oncostatin M, and interferon-γ (INF-γ) genes [17-20]. It is also noteworthy that the most recent non-surgical treatment of RA pathology arose from deciphering how these pro-inflammatory cytokines activate the various signaling pathways deemed to be relevant to RA pathogenesis and disease progression. Thus over the past 20 years or so there occurred the development of several TNF-blocking monoclonal antibodies and a TNF dimeric-fusion protein [21], an IL-1 receptor antagonist protein (IRAP) [22], a cytotoxic lymphocyte antigen-4 Immunoglobulin [23], a monoclonal antibody that neutralizes IL-6/IL-6 receptor interactions [24] and the first small molecule inhibitor of Janus kinase-3 (JAK3), namely, tofacitinib, [25-27]. In fact, the pharmacologic basis for the clinical efficacy of tofacitinib in the treatment of RA in patients who have inadequately responded to methotrexate-induced immunosuppression resides in the capacity of tofacitinib to suppress STAT protein phosphorylation [28].

Continuously activated JAK/STAT has been described for a variety of cancers, including, lymphoma, leukemia and myeloproliferative diseases [29,30], solid tumors [31] as well as in immunodeficiency syndromes such as HIV-1 [32]. In addition to continuous activation of JAK/STAT, a family of proteins, called, suppressor of cytokine signaling (SOCS) proteins, were also found to be up-regulated in response to STAT protein activation.

SOCS are potent endogenous negative regulators of JAK/STAT pathway signaling [4, 33-35] which are critical for both the positive and negative control of macrophage and dendritic-cell activation [36] and other cells involved in innate and adaptive immunity. Recently, Arnold *et al.* [37] showed that the macrophages which infiltrated inflamed glomeruli in a rodent model of acute nephritis contained increased levels of SOCS-3. In addition, SOCS-3 was co-localized with the macrophage pro-inflammatory M1 phenotype, the latter characterized by elevated levels of IL-1β, IL-6, IL-23 and IL-12 production.

Several forms of SOCS have been identified. The intracellular family of SOCS proteins is comprised of 7 forms of SOCS (*i.e.,* SOCS-1 - SOCS-7) and the cytokine inducible SH-2 domain protein (CIS, now also referred to as CISH). All of these proteins share a central SH2 domain and a conserved C-terminal SOCS box domain [4]; the latter SOCS box domain acting as a critical structural component for directing activated STAT proteins to the ubiquitin-transferase degradation pathway [38]. At approximately the same period following the discovery of the SOCS/CIS family of proteins, several research groups showed that persistent cytokine-mediated signaling through JAK/STAT was regulated by SOCS/CIS [39, 40], with 2 SOCS family members, SOCS-1 and SOCS-3, prominently implicated in regulating STAT protein activation via their capacity to positively bind to the tyrosine-containing regulatory domain of JAK through its SH2 domain [4, 41]. Moreover, additional evidence demonstrated that pro-inflammatory cytokines differentially induced various SOCS and/or CIS proteins [42]. Thus, IL-6 was shown to induce SOCS-1, whereas TNF-α induced SOCS-3, and INF-γ induced SOCS-1 and SOCS-3, in addition to SOCS-2 [43], with recent evidence from Mahony *et al.* [44] supporting the view that SOCS-3 was the most influential SOCS protein family member with regard to its role as a cytokine and pathogen-induced signaling molecule.

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Signal Transduction and Autoimmunity

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Of note, the regulation of SOCS family gene expression was shown to be under the rigorous control of activated (*i.e.,* phosphorylated) STAT proteins which completed the negative feedback loop for SOCS gene expression. In fact, the most likely mechanism responsible for negative regulation of JAK/STAT pathway activation appeared to be that SOCS/CIS binding to JAK was a requirement for recruiting and activating STAT proteins [45], although ubiquitination was also likely to be involved [38].

Two studies, in particular, demonstrated the several mechanism(s) involved in the negative regulation of STAT protein activation. Thus, examining the structure of the SOCS-1/JAK2 complex showed that SOCS-1 bound directly to JAK *via* SH2 [46], whereas SOCS-3/SH2 domain bound directly to the cytokine receptor [41]. Importantly, Pirvulescu *et al.* [47] showed an association between the silencing of STAT3 using STAT3-specific silencing RNA and the suppression of SOCS-3.

Studies conducted in SOCS knockout mice have also proved to be revealing with respect to how SOCS-1 regulated INF-γ, IL-4, IL-12 and IL-15 during T-cell activation [42]. For example, wild-type SOCS-1 mice were shown to be hypersensitive to the administration of INF-γ and lipopolysaccharide (LPS) for STAT target gene activation [48]. More recently, Marijnissen *et al.* [49] showed that SOCS-1 and SOCS-3 inhibited TLR signaling in response to IL-21 when adjuvant-induced arthritis was induced in IL-21 receptor deficient (IL-21$^{-/-}$) mice the response of which was then compared to wild-type mice. Thus, IL-21$^{-/-}$ mice were significantly impaired with respect to their capacity to produce SOCS-1 and SOCS-3 mRNA compared to their wild-type counterparts.

Shouda *et al.* [50] had originally proposed that SOCS-3/CIS-3 were the most critical SOCS protein family members for RA. As such modulation of SOCS-3/CIS-3 activity could be envisioned as a potential therapeutic intervention for RA and other autoimmune diseases. This assertion was based mainly on the results obtained from studies in 2 rodent models of experimental arthritis induced by adjuvant or Type II collagen. In addition, Shouda *et al.* [50] showed that over-expression of SOCS-3 inhibited synovial fibroblast proliferation and IL-6 production which appeared to be dependent on activation of JAK/STAT signaling [4]. This finding led to several lines of investigation in which a dominant-negative form of STAT3 was employed to suppress induction of arthritis. However, perhaps unexpectedly, the SOCS-3 construct proved to be more effective that the dominant-negative STAT3 construct for preventing joint damage [50].

Then, in 2007, Isomäki *et al.* [51] showed that patients in the active stage of RA showed "profound" changes in the level of SOCS isolated from the various immune cell types in RA synovial tissue. In that regard, SOCS-1 and SOCS-2 levels were elevated in T-cells recovered from the peripheral blood of RA patients, whereas SOCS-1 and SOCS-3 were the dominant SOCS isoforms in RA synovial tissue macrophages, although the majority of these macrophages were immunochemically classified as SOCS "negative." Another study [52] was apparently designed to confirm and then extend the findings of Isomäki *et al.* [51]. Here, the transcript levels of SOCS-1, SOCS-2, SOCS-3 and CIS in peripheral blood mononuclear cells (PBMC) from RA patients and patients diagnosed with active systemic lupus erythematosus (SLE), were measured and compared to a control group [52]. Active SLE patients had elevated SOCS transcript levels, while, SLE patients in remission classified as "inactive" did not. Of note, SOCS/CIS transcript levels in active RA patients did not differ from normal individuals, although treatment of patients with active RA using TNF blockade appeared to increase CIS transcripts. This finding suggested that CIS may be the more suitable biomarker of the SOCS protein family when evaluating the clinical response to TNF blockade. Importantly, the finding that SOCS transcript levels in RA PBMC did not differ from those found in normal PBMC may also reflect the significant number of SOCS "negative" macrophages reported by Isomäki *et al.* [51].

The results of additional recent studies have also been illuminating with respect to the role of SOCS/CIS as a regulator of arthritis and Sjögren's syndrome pathology. In one study van de Loo *et al.* [53] examined SOCS/CIS levels in chondrocytes isolated from human OA and RA cartilage, while in another Vartoukian *et al.* [54] measured SOCS/CIS levels in salivary gland cells from patients with Sjögren's syndrome which was compared SOCS/CIS levels in patients who presented only with sicca complex.

The level of SOCS-3 mRNA, but not SOCS-1 mRNA, was elevated in OA and RA chondrocytes compared to chondrocytes isolated from the cartilage of individuals who had sustained a femoral neck fracture [53]. Importantly, SOCS-3 mRNA was associated with an increase in matrix metalloproteinase-13 (MMP-13), a disintegrin metalloproteinase with thrombospondin motif-4 (ADAMTS-4) and ADAMTS-5 mRNA which represents two enzyme classes intimately associated with arthritis pathology. However, SOCS-3 RNA was not associated with Type II collagen (COL2A1) gene expression. Interestingly, over-expression of SOCS-3 by normal bovine chondrocyte cultures resulted in a reduction in IL-1 and LPS-induced nitric oxide production as well as in insulin-like growth factor-1-induced proteoglycan synthesis indicating that SOCS-3 is likely to have pleiotypic effects on chondrocyte homeostasis.

With respect to the effect of activating JAK/STAT by recombinant human (rh) IL-6, we recently showed that rhIL-6 increased MMP-9 (i.e. 92kDa gelatinase) production in 2 lines of immortalized human chondrocytes [55]. Moreover, production of MMP-9 was significantly reduced by tocilizumab, a fully humanized monoclonal antibody which neutralizes the interaction between IL-6 and IL-6Rα [24], as well as by the combination of rhIL-6 and soluble IL-6 receptor. In another study referred to previously, Vartoukian *et al.* [54] showed that SOCS-3, phosphorylated STAT3 (p-STAT3) and IL-17 in PBMC and salivary gland cells was increased in response to IL-6 in patients with Sjögren's syndrome, the results of which were compared to the sicca control group where these cells mainly expressed SOCS-3 *or* IL-17. Thus, SOCS-3 levels were enhanced in Sjögren's syndrome, although the absence of the expected inverse relationship between SOCS-3 and p-STAT3/IL-17 in these patients appeared to also indicate a "functional disturbance" in the JAK/STAT signaling cascade. Thus, this relationship suggested a reduction in function rather than a reduction in the expression of the SOCS-3 gene which was likely to account for the deregulated production of IL-17.

Based on the results of these many basic laboratory and animal studies, one could make a reasonable assumption that there would be a drug developed which would target SOCS/CIS proteins and be used as a potential therapeutic intervention for RA or other autoimmune disorders. However, as this review was being prepared a search of the PubMed database using the term, "SOCS/Clinical Trials" failed to identify any published clinical trials studies involving SOCS and RA or autoimmune disorders. However, another search tool which employed the clinicaltrials.gov database and the search term, "suppressor of cytokine signaling *and* cancer" identified a clinical trial (clinical trials.gov identifier, NCT02688686) which, has not yet

begun to recruit subjects. However, the stated purpose of this phase I/II study was to evaluate "the safety and efficacy of a dendritic cell (DC) vaccine combined with cytokine-induced killer cells in patients with advanced non-small-cell lung cancer with bone metastases." On the clinicaltrials.gov website the clinical trial design was stated to involve the use of experimental DC transfected with an adenoviral-5 vector coding mRNAs including SOCS-1, mucin-1 cell-associated mucin (MUC1) and survivin. However, no proposed or ongoing clinical trials were found on the clinicaltrials.gov website for autoimmune disorders using an identical search tool strategy but employing the terms, "suppressor of cytokine signaling *and* rheumatoid arthritis, SLE, Sjögren's syndrome, Type I diabetes". Therefore, at this time while there appears to be compelling evidence linking SOCS/CIS to functional deregulation associated with several immune cell defects in RA and other autoimmune disorders this has not appeared to have resulted in a concerted effort to develop a drug that would potentially impair pro-inflammatory cytokine-induced JAK/STAT pathway activation in RA via a strategy that might boost SOCS/CIS-mediated negative regulation of JAK/STAT.

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