

Somatostatin Involvement in Rheumatoid Arthritis

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Abstract: Somatostatin (somatotropin release inhibitory factor; SRIF) peptides are widely distributed in the mammalian body and, acting through a family of genetically homologous cell surface receptors (sst₁₋₅), regulate cellular secretion and proliferation. Compelling evidence implicates SRIF peptides and peptidyl analogues in chronic inflammatory diseases such as rheumatoid arthritis (RA). SRIF membrane receptors exist on immune and synovial cells, thereby providing molecular targets on the principal participants in the RA pro-inflammatory cascade. Preclinical and clinical studies have shown that SRIF peptides and analogues are anti-inflammatory, however the cellular basis for this activity remains unclear. Since RA inflammation is propagated through cell-mediated immune responses which orchestrate the pro-inflammatory cytokine production by monocytes, macrophages and synovial fibroblasts, SRIF could provide a strategy for interrupting RA progression. SRIF and SRIF analogues reduce synoviocyte proliferation and suppress synovial cytokine production, thereby making SRIF analogues a potentially novel approach to RA treatment. This review summarizes our current knowledge of SRIF analogue therapies in RA.

INTRODUCTION: RHEUMATOID ARTHRITIS AND INFLAMMATION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive disability and a reduction in life expectancy [1, 2]. The inflammatory progress of RA relies upon intercellular communication between activated, immigrant immune cells and the resident cells of the affected joint. Secreted immune mediators serve to propagate the inflammatory process with cell-mediated events ultimately promoting cartilage damage [1]. The destruction of cartilage and bone are hallmarks of chronic RA.

Conceptually, the arthritic process develops through a cell-mediated immune response with the infiltration of CD4+ T lymphocytes into the synovial membrane. The participation of CD4+ lymphocytes is supported by genetic studies which link RA with histocompatibility-complex class II antigens, as well as clinical observations that suggest a prominent role of immune mediators in promoting RA development [3, 4]. Soluble cytokine mediators are crucial to the arthritic process with tumor necrosis factor α (TNF- α) and interleukin 1- β (IL-1 β) providing primary inflammatory roles in disease development. However, studies have also highlighted the important role of synovial macrophages in the pathogenesis of RA and that changes in CD68+ cells in the synovial sublining may be a possible biomarker to predict arthritis treatment efficacy [5]. These synovial macrophages are highly activated and secrete copious amounts of the pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α) and interleukin 1 β (IL-1 β), providing primary inflammatory roles in disease development. While cytokine roles may differ in arthritis progression, both IL-1 β and

TNF- α participate in the development of RA joint damage [1].

In addition to the resident macrophage cells of the joint [5] resident fibroblast dysfunction appears to be involved early in RA development and is associated with inflammation [6]. RA synovial inflammatory events include capillary formation, synoviocyte hypertrophy and a hyperplastic synovial membrane development which results directly from the activation of the Type 2 (fibroblast-like) synoviocytes [1,7]. At the synovial level cytokine involvement has proven to be complex, with the RA fibroblast synoviocyte actively promoting the inflammatory process [7, 8]. Synoviocytes release a spectrum of mediators, including chemoattractant mediators such as macrophage chemoattractant protein (MCP-1), pro-inflammatory effectors such as leukemia inhibitory factor (LIF) and IL-6, angiogenic promoting effectors, such as platelet-derived growth factor (PDGF), in addition to enzymes, such as metalloproteinases (MMP) collagenase (MMP1) and stromelysin (MMP3) that promote matrix degradation [8]. In addition, the synovial fibroblasts secrete growth factors which regulate hematopoietic cell growth and differentiation, as well as promoting the expression of cellular adhesion molecules. Indeed, synoviocyte and immune cell intercommunication drives RA progression as leukocyte deposition within the synovium aids in the release of inflammatory cytokines, chemokines and degradative enzymes.

A number of pharmacological agents have proven useful in controlling RA, such as soluble cytokine receptor proteins and humanized monoclonal antibodies, but effective long-term management has proven difficult, even with recent changes in disease diagnosis and aggressive early treatment [1, 9]. Clearly, therapies that regulate arthritic inflammation by controlling synoviocyte activation, suppressing immune cell cytokine release and inhibiting degradative enzyme expression would be valuable in controlling RA progression.

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SOMATOSTATIN AND RHEUMATOID ARTHRITIS

Inflammatory responses in the arthritic joint are controlled through a complex intercellular communication between synoviocytes and immune cells, where pro-inflammatory chemokines and cytokines initiate and propagate the response [1, 2]. Understanding the regulation of one or more of these interactions may allow intervention in the RA injury cycle. It has become clear that the body's endogenous hormones can influence responses to inflammatory events. For example, steroid hormones, such as the ovarian steroid estrogen, play a significant role in regulating the body's inflammatory responses [10]. Endogenous peptides also control inflammatory responses, and evidence exists that peptides such as corticotropin releasing hormone and substance P are pro-inflammatory [11, 12]. Several peptide families have been shown to possess possible anti-inflammatory activities, including calcitonin gene-related peptide, vasoactive intestinal peptide and SRIF [13-15]. Although SRIF was originally identified as a neuroendocrine regulator of growth hormone (GH) secretion [15], SRIF peptides are now known to be involved in a spectrum of physiological activities [17, 18].

SRIF is produced at sites of inflammation [19] and although the cellular origin of the produced SRIF remains unknown, a number of immune cells are known to secrete SRIF family peptides. SRIF peptides have a documented immunomodulatory role and furthermore, SRIF immunoreactivity has been demonstrated in bone and joint tissues [20, 21]. SRIF and SRIF peptide analogues exert anti-inflammatory effects in preclinical and clinical studies [15, 20, 22]. These anti-inflammatory actions are thought to be direct and receptor-mediated [15, 23]. Despite several studies showing SRIF's anti-inflammatory actions in animal models and humans, the cellular target and intracellular mechanism by which SRIF reduces inflammation remains unclear, although the inhibition of inflammatory mediator secretion may be involved [13, 19, 21].

Somatostatin Receptor Subtype Pharmacology and Physiology

SRIF is widely distributed throughout the body and SRIF peptides can be readily detected in human serum [24]. Somatostatin exists as two discrete peptides in the mammalian body, SRIF-14 and SRIF-28, both of which are derived from a 116 amino acid precursor, pre-prosomatostatin. A recently discovered neuropeptide, cortistatin has expanded the SRIF peptide family [25]. Cortistatin displays a unique tissue distribution, separate from that of the SRIF-14 and -28 peptides. Cortistatin shares 11 of the 14 amino acids found in SRIF-14 and binds with high affinity to all known SRIF receptors, in addition to possessing a lower affinity for the growth hormone secretagogue receptor [25]. Cortistatin is produced in a broad spectrum of human tissues, including the mononuclear cells of the blood, suggesting that cortistatin, rather than SRIF, may be the principal ligand for immune cell SRIF receptors [26].

SRIF peptides elicit their biological effects through specific, high affinity interactions with a family of five highly conserved, integral membrane receptors (sst1, sst2A, sst2B, sst3, sst4, sst5; 27). SRIF receptor genes lack introns, with the exception of the sst2 gene which contains a cryptic splice site that produces the unique carboxyl terminal variants,

sst2A and sst2B [27]. SRIF receptors are heterogeneously expressed throughout the body and multiple receptor subtypes can coexist at the cellular level [18]. All SRIF receptors belong to the guanine nucleotide-binding protein-coupled receptor (G protein-coupled receptor; GPCR) superfamily, whereby agonists ligate and activate the receptor, resulting in an intracellular signaling pathway that communicates, *via* G protein subunits, to the appropriate intracellular effectors [27]. SRIF receptors communicate the peptide's responses to the cell's interior *via* the pertussis toxin sensitive family of inhibitory G protein α subunits (G_i/G_o) in addition to the toxin insensitive G proteins G_{aq} , $G_{\alpha 14}$ and $G_{\alpha 16}$.

SRIF receptors couple extracellular peptide binding to multiple intracellular effector enzymes [17, 18]. All five SRIF receptors inhibit adenylyl cyclase activation, resulting in the suppression of 3',5' cyclic adenosine monophosphate production [18]. Depending upon the cellular context, SRIF receptors can also control membrane ionic conductances, regulate phosphoprotein tyrosine phosphatases and selectively activate other transduction effectors such as phospholipase C, phospholipase A2 and the extracellular regulated protein kinase family [17, 18]. Cell line studies employing endogenously or heterologously expressed receptors have established that SRIF *in vitro* action is predominately inhibitory, resulting in the suppression of hormone secretion and reductions in cell proliferation [17, 18].

Recently, cell-based studies have shown that different SRIF receptor subtypes are capable of dimerizing, with significant differences noted between these co-expressed receptor subtypes [28]. For example, biochemical studies have shown that SRIF ligand activation of the sst5 receptor shifts the basal monomeric form of the receptor to a higher molecular weight oligomeric configuration [28]. And while sst2 and sst3 are both capable of homodimerization, the sst1 receptor does not undergo a similar change in protein-protein association [29]. The functional consequences of receptor dimerization are apparent when heterodimerization studies have been performed. For example, heterologous expression studies using transfected human embryonic kidney cells demonstrated that sst2 heterodimerization with sst3 effectively inactivated the sst3 function, while retaining the pharmacology and function of the sst2 receptor subtype [31]. These results suggest that receptor dominance may occur when two or more SRIF receptor subtypes are endogenously co-expressed in individual cells, resulting in differences in receptor function and desensitization [31, 32]. Indeed, depending upon the cell under study, endogenously expressed SRIF receptor subtypes can couple to multiple intracellular signaling pathways which functionally overlap [32]. While it is unclear why cells express multiple SRIF receptor subtypes, receptor co-expression might differentially regulate cellular function, such as through receptor subtype silencing, or provide additional mechanisms which could be clinically exploited in controlling chronic inflammatory diseases, such as RA [18].

Endogenous SRIF peptides are labile thereby significantly limiting the clinical utility of the native peptides. Given that SRIF peptides have a serum half-life of approximately three minutes, considerable effort has been directed at producing more stable analogues and peptidomimetics (reviewed in [17, 33]; Table 1). The initial observation that the

Table 1. SRIF Receptor Peptide Ligand Binding Affinities (IC₅₀, nM) and Serum Half Life (T_{1/2})

Agonist	sst ₁	sst ₂	sst ₃	sst ₄	sst ₅	T _{1/2}
SRIF-14	0.93	0.15	0.56	1.5	0.29	3 min
Octreotide	280	0.38	7.1	>100	6.3	2 h
Cortistatin	0.25-0.70	0.60-0.9	0.4-0.6	0.5-0.6	0.3-0.4	NA

SRIF-14, Octreotide and human cortistatin-17 binding affinities given are provided as IC₅₀ (nmol l⁻¹) for the cloned and heterologously expressed human sst1-5 (taken from [17,18, 25]). NA – not available.

four amino acids present at the peptide's β -turn are required for biological activity led to the initial development of SRIF analogues of reduced ring size and increased metabolic stability [34]. Analogues to SRIF have been developed with synthetic peptide agonists and antagonists, as well as non-peptidyl agonists and antagonists having been developed over the last decade [17]. Octreotide and Lanreotide are SRIF octapeptide derivatives that possess the highest binding affinity for the sst2 receptor subtype, followed by weaker binding to the sst3 and sst5 subtypes [17]. Octapeptide analogues of SRIF remain the only therapeutic agents currently available, although additional SRIF analogues, including agonists that recognize the sst4 receptor subtype, have recently been reported to be in Phase 1 studies [17].

Somatostatin Effects on the Immune System

Since the original identification of SRIF binding sites on human monocyte and lymphocyte membranes [35] a role for SRIF peptides in the immune system has emerged [21]. SRIF receptors and peptides appear to be widely expressed on rodent and human immune cells and play a role in controlling immune cell function [21]. Recent studies have clarified the location of SRIF receptor subtypes in the immune system and demonstrated a differential expression of receptors in peripheral immune cells. While earlier studies pointed to SRIF-14 as the primary signaling peptide [21], a recent study has documented the presence of the SRIF family member cortistatin as the sole SRIF peptide produced by peripheral immune cells [26].

A differential expression of SRIF receptor subtypes was recently noted in immune cells, thereby providing the molecular identities to the earlier radioligand binding studies of Bathena and colleagues [35]. Using reverse transcriptase-polymerase chain reaction (RT-PCR) and quantitative PCR (Q-PCR) protocols on blood drawn from healthy volunteers, Lichtenauer-Kaligis and colleagues established the SRIF receptor subtypes found *in vivo*. In total blood peripheral mononuclear cells (PBMC) the presence of both the sst2A and sst3 receptor subtypes was noted [26]. Sub-fractionation of the PBMC population with selective antibodies (CD2 or CD3 for T cells, CD19 for B lymphocytes and CD14 for monocytes) revealed that both T-lymphocyte and B-lymphocyte populations solely expressed the sst3 receptor subtype. In contrast, freshly isolated monocytes were devoid of receptor subtype expression until cellular activation, upon which the sst2A subtype was detected [26].

Using a combination of a fluorescent SRIF analogue, fluosomatostatin, and fluorescence activated cell sorting (FACS) Lichtenauer-Kaligis and colleagues further established that the monocyte sst2A receptor subtype was ex-

pressed on the cell surface, which was in marked contrast to the B and T cell receptors [26]. These FACS results, taken together with previous pharmacologic and functional studies on SRIF activities in leukocytes, suggest that the receptor binding sites that have been detected on immune cells may be derived from a monocytic lineage and reflect the degree of activation to which the cells were subjected.

It is noteworthy that the presence of sst2A expressing monocytes provides a molecular target for SRIF analogue therapies. Since sst2A receptors have been shown to inhibit hormone secretion in a range of cellular and physiological studies [18, 36] and given the proposed role of monocytes in rheumatoid arthritis [37], the findings of Lichtenauer-Kaligis and colleagues suggest that the role of SRIF peptides in modulating inflammation might be tied to their cellular actions on monocytes [26]. Clearly, a role for SRIF control of monocyte pro-inflammatory mediator secretion would be consistent with recent clinical results [38].

Somatostatin Effects on the Synovium

Animal models have proven invaluable in demonstrating the utility of SRIF peptides and analogues in RA [38]. Pre-clinical studies show that physiologic concentrations of SRIF inhibit synovial proliferation, as well as cytokine and MMP production [38]. The normal synovial membrane consists of a discrete intimal lining and a synovial sublining, with both linings containing a sparse population of blood vessels, adipocytes and fibroblasts [39]. Normally the resident cells in the joint are topographically separated from the immigrant immune cells, however, the inflammatory events of RA serve to promote immune cell interactions with the synovial cells. In RA, the cellular composition of the synovial membrane changes markedly as the intimal layer thickens and invading lymphocytes, leukocytes and macrophages intermix with resident fibroblasts. The synovial lining is the target for a number of inflammatory events, including leukocyte diapedesis, synovial proliferation, and cytokine and matrix metalloproteinase (MMP) production. Synovial fibroblasts are directly implicated in the RA inflammatory cascade and provide an effector role in RA pathogenesis [7, 40]. Indeed synovial fibroblasts produce a spectrum of effector molecules which control angiogenesis and chemoattracton, modulate inflammation, and participate in bone remodeling [8].

In their pioneering study on SRIF actions in the rheumatoid synovioyte, Takeba and coworkers obtained synovial tissues from patients that were undergoing joint surgery [13]. RT-PCR experiments illustrate both sst1 and sst2 mRNA in RA HFLS, with sst2 expression up-regulated upon pro-inflammatory challenge with TNF α [12]. Immunohistochemical studies revealed sst2A expression on both fibroblast-like and macrophage synovioytes [38, 39]. Further-

more, synovial cells isolated from the inflamed synovium of patients with RA have been shown to produce SRIF mRNA, suggesting that pro-inflammatory challenge up-regulates SRIF peptide expression [13].

The results of *in vitro* studies in tissues and isolated cells are in good agreement as sst2A mRNA and protein was detected in RA synovial tissue biopsies, and the presence of a functional sst2A receptor was demonstrated in cultured synoviocytes prepared from RA synovial membranes [38]. Indeed, a functional assessment of SRIF synovial actions shows a range of activity, including a reduction in the mRNA levels for the cytokines TNF- α and IL-1 β . Because SRIF is produced by, and acts on the synovium, a novel autocrine system is in place for controlling the developing pathology. It is obvious that local SRIF production is not sufficient to control the deleterious effects of RA which are consistently reinforced by the aggressive pannus. SRIF treatment targeting the synovium *in vivo*, may provide a novel mechanism for controlling progressive RA by controlling the production of bone and cartilage degrading enzymes.

Clinical Studies of SRIF and RA

The clinical relevance of SRIF receptor expression has been demonstrated in a small cohort of patients with immune-mediated diseases and, based upon these studies, a neuroendocrine pathway for SRIF modulation of immune responses has been proposed [39, 40]. Indeed, a recent study has shown that serum SRIF levels in RA patients, aged 55 or older, were significantly reduced when compared to age-matched control subjects [41], suggesting that a reduction in circulating SRIF may accompany the progressive inflammation seen in RA. Taken together, these results suggest that reductions in circulating SRIF peptide levels may be linked to RA and other chronic inflammatory diseases [39].

Early clinical data on the role of SRIF as an important anti-inflammatory peptide, came from the observation that removal of a symptomatic somatostatinoma, which was associated with a 60-fold increase of the serum SRIF concentration, led to normalization of the serum level of SRIF and new onset RA [42].

In a study of sixteen patients with RA, intra-articular (IA) injection of SRIF-14 reduced synovial thickness in affected knees [43]. Patients were injected with 6 IA injections of 750ug of somatostatin-14 (SRIF-14) at 15-day intervals and synovial thickness was serially measured by musculoskeletal ultrasound. The synovium of the contralateral knee was also studied, in order to ascertain any possible systemic effects of the local injection. The normal knee has a synovial membrane thickness of about 3.0mm to 3.5mm. A significant reduction in synovial membrane thickness was observed by the third treatment in 14/16 patients and the effect of the treatment continued to be evident by the fifth or sixth injection. The mean pre-treatment synovial thickness of the arthritic knee was 4.81mm, which decreased to 3.75mm and 3.5mm by treatments 3 and 6, respectively. Additionally, the synovial thickness of the contralateral knee (not injected with SRIF-14) was similarly decreased in 8 out of 16 patients. The investigators postulated that SRIF-14 can potentially reduce synovitis *via* both a local and a systemic mechanism [43].

The use of SRIF-14 as a joint inflammation modulator has been studied in another study, as well [22]. Forty-one patients with RA were treated with IA injections of 750ug of SRIF-14 every 15 days for a total of 6 injections. The patients had active RA and were being treated with disease modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), although no corticosteroids were administered. Efficacy parameters used included pain (at rest and movement), joint tenderness, morning stiffness and spontaneous pain, while simultaneously measuring acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Tele-thermography was also used to measure joint inflammation. Safety assessment included evaluation of liver enzymes and renal function before and after treatment. SRIF-14 was efficacious in reducing joint inflammation; reduction in pain at rest and movement was already significant by the second treatment. By the third treatment improvement in all clinical parameters was noted. There were no local or systemic side effects reported which led to the conclusion that SRIF-14 was a well tolerated and effective treatment alternative in reducing joint inflammation and pain in RA, with improvement seen as soon as after one month of treatment [22].

However, SRIF native peptides (SRIF-14 and SRIF-28) are highly labile with a short serum half-life and agonist effects at all five SRIF receptor subtypes, thereby limiting the peptide therapeutic utility. The development of stable subtype selective ligands has sought to overcome the limitation of the endogenously produced agonists [17, 18]. The efficacy and safety of a long acting SRIF analogue, octreotide was evaluated in a pilot study for the treatment of refractory RA [44]. Ten patients with refractory RA, who had failed treatments with at least 4 DMARDs, received monthly intramuscular (IM) injections for 3 months. The measure of clinical response was based on the American College of Rheumatology criteria of 20% improvement in measures of disease activity (ACR-20). Clinical efficacy endpoints used were number of tender and swollen joints, global assessment of disease by the physician and patient, patient evaluation of pain using the visual analogue of pain scale, and physical function. Laboratory values measured monthly were ESR and CRP. Eight of the 10 patients completed the trial, while 2 of the patients received only 2 doses of the injection. Four of the patients met the ACR-20 criteria at weeks 6-10 and two of these patients continued to improve with time and met the ACR-50 and ACR-70 criteria respectively. All 10 patients experienced some improvement in mean visual analogue scales for pain, number of swollen joints and global assessment of the physical disease activity. There was a trend towards a decrease in ESR and CRP values. In terms of side effects, one of the patients reported urticaria that resolved after discontinuation of the drug and one of the patients had a minor transient increase in liver enzymes. Other side effects noted were minor bloating and loose stools that resolved for most patients with time and low fat diet nevertheless one patient had severe diarrhea that led to weight loss which resolved after ceasing the drug. This study supported the notion of a possible beneficial effect of long acting SRIF in refractory RA, a treatment that was relatively well tolerated [45]. In another open label, pilot study from Turkey, 11 DMARD-resistant RA patients received daily subcutaneous

(SC) injections of 0.1mg octreotide [44]. Seven patients completed the 8-week treatment course, 2 patients were withdrawn after a 4-week course, while the remaining 2 dropped out early because of side effects (intractable diarrhea and elevation of fasting blood glucose, respectively). Clinical improvement was observed in outcomes such as pain, physician's and patient's global assessment of disease activity, and mean number of swollen joints. Again, there was only a trend toward a decrease in ESR and CRP values [44]. Unfortunately, no controlled studies followed either pilot study and, therefore, this observation could not be verified.

The use of growth hormone to SRIF ratio in RA may be a useful marker in assessing disease activity in patients with active RA. In a recent study, basal serum growth hormone (GH), insulin like growth factor (IGF-1) and SRIF concentrations were measured using standard immunoassays in RA patients [41]. RA patients had elevated serum growth hormone and decreased SRIF, although similar IGF-1 levels in comparison to age matched individuals. The growth hormone to SRIF ratio was skewed upward in RA patients when compared to age matched controls, making it a potential disease activity marker. Furthermore, it supports the notion that increasing SRIF levels or using the currently available subtype selective SRIF analogues, as adjuvant therapy in RA, may be beneficial. There may be a particular benefit in using SRIF therapy locally (e.g. IA) in RA; a recent study found a 3-fold increase in GH in RA synovial fluid, compared with RA serum. Furthermore, recent studies suggested that long-standing RA treatment with SRIF may suppress GH burst frequency and mass in normal men [41, 46- 47].

SRIF analogues have proven effective in receptor imaging studies and van Hagen and colleagues explored *in vitro* and *in vivo* expression of SRIF receptors on synovial membranes of patients with RA [40]. The joints of 14 patients with RA and 4 with severe osteoarthritis were compared to the joints of 30 control patients. The SRIF analogue (¹²⁵I Tyr3)-octreotide was used for *in vitro* SRIF receptor autoradiography and (¹¹¹In-DTPA-D-Phe1) -octreotide was used *in vivo*. The lesion related sensitivity in 76% of swollen joints in RA and this correlated well with the degree of pain and swelling. The radioactivity was much lower in osteoarthritis patients and not found at all in control patients, making this particular form of scintigraphy a potentially useful diagnostic tool. Another study on the role of octreotide scintigraphy in RA (and also in sarcoid), further supported the notion that scintigraphy might be a useful diagnostic tool to monitor disease activity. It was also proposed that the radiolabeled SRIF receptor analog could be injected in severe cases of RA, where the SRIF analog could help suppress hyperproliferating pannus formation [48].

SRIF analogues could prove useful in the long-term management of RA. The heterogeneity of RA and the variability in patient responses makes it likely that effective disease management will require multiple approaches, as well as the development of new RA therapies [9, 49]. While biologics have proven to be an effective therapy for controlling severe RA, cost, safety concerns and long-term loss of efficacy have tempered the early enthusiasm for this therapy class [49]. Agents such as SRIF may prove to be a useful additional therapy, given the low incidence of side effects

that have been reported in the small number of clinical studies. Emerging ideas on SRIF actions suggest that new medical applications for SRIF may be forthcoming [36]. Ideally, defining the cellular target(s) of SRIF action in diseases such as RA may provide new and more effective strategies for the control of chronic disease conditions.

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