



The role of insulin growth factors in autoimmune diseases

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Abstract: Insulin-like growth factors (IGFs), their receptors and their binding proteins form a distinct bioregulation system that regulates growth, cell proliferation, apoptosis and tissue remodeling. Recent data highlight a significant interaction of IGFs and the components of the immune system, especially B and T cells. Accumulating data suggest an important role of IGFs in autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc) and Sjogren's syndrome (SS). Herein, we summarize the current evidence on the role of IGF pathway in immune system regulation as well as its potential involvement in the pathophysiology of systemic autoimmune diseases.

Keywords: Autoimmune diseases; immune system; insulin-like growth factors (IGFs); Sjogren's syndrome (SS)

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Introduction

The insulin-like growth factor (IGF) pathway includes IGF (IGF-I and IGF-II), insulin-like growth factor binding proteins (IGFBPs) and insulin-like growth factor receptors (IGF-IR and IGF-IIR) (1,2).

IGFs play key roles in normal growth, metabolism and homeostasis of organisms. Their main production site is in the liver under the control of growth hormone (GH). The detection of their differential expression in pathological conditions, such as cancer, cardiovascular and metabolic diseases, has stimulated researchers' interest in designing new and promising therapeutic approaches (3,4).

Several recent studies reveal the interaction of IGF pathway with the immune system. IGFs' detection at mRNA and protein level in peripheral blood mononuclear cells, the interaction of the growth factor pathway with various cytokines (e.g., interferons) and immune cells such as T lymphocytes, macrophages and bone marrow cells, are only few examples (5-7). Moreover, dysregulation of the IGFs pathway in the setting of various autoimmune diseases, such as type I diabetes, Grave's disease, Crohn's

disease, rheumatoid arthritis (RA) and Sjogren's syndrome (SS), implies a potential contributory role of IGFs in autoimmune pathogenesis (8-17).

The aim of the present review is to summarize the available literature regarding the role of IGF pathway in immune system regulation as well the pathophysiology of systemic autoimmune diseases.

IGF-1 gene: localization and isoforms

The human *IGF-1* gene is located in the long arm of chromosome 12, contains six exons and gives rise to three mainly heterogeneous transcripts: Ea, Eb and Ec- through a combination of: (I) alternative use of promoters, (II) alternative splicing and (III) different polyadenylation signals (18,19).

These IGF-I transcripts encode three different peptides, which also undergo post-translational modification. IGF-I Ea transcript derives from the splicing pattern exon 1 or 2-3-4-6 of the *IGF-1* gene represents the main IGF-I mRNA produced by the liver and other tissues as well, with similar exon sequence (20,21). IGF-I Eb transcript

is a splice variant of exon 1 or 2-3-4-5. Its expression was initially detected in human liver (22), while it was also found to be expressed, in skeletal muscle and other various tissues and cells such as prostate and endometrium (19). IGF-I Ec transcript is an exon 1 or 2-3-4-5-6 splice variant of the *IGF-1* gene. Structurally, the IGF-I Ec mRNA transcript differs from the IGF-I Ea variant by the presence of the first 49 base pairs from exon 5. IGF-I Ec mRNA transcript was initially identified in human liver, however, it is expressed at approximately 10% of the main IGF-I Ea transcript (21). This transcript was named mechano-growth factor (MGF) since it was found to be upregulated in response to muscle stretch and/or damage (23). Of interest, its expression has been also identified in various tissues such as endometrium (24), normal and cancerous prostatic cells (25), as well as in osteoblast-like osteosarcoma cells (26,27). Its regulation appears to be under IL-6 action (28).

The different IGF-I mRNA transcripts encode its precursor proteins, which differ in length of their amino-terminal peptide (signal peptide) and the structure of peptide E (extension peptide or E domain) at their final end. The last four (4) amino acids in the C region appear to be responsible for the strong affinity (binding) to the IGF-IR receptor and the transmission of its signal (19,29). The biological significance of splicing variants of the IGF-I gene is unknown and the molecular and physiological mechanisms regulating their expression are uncertain, however, these variants probably indicate the complexity of IGF-I activities through its different isoforms (18).

Insulin growth factor binding proteins and their biological role

IGF I and II are mainly produced by the liver under the action of GH which is secreted by the pituitary gland. The availability of IGF-I for binding to its receptor is determined by its interaction with the binding proteins. Six main types of insulin growth factor binding proteins (IGFBPs 1–6) has been identified which display very high affinity for IGF-I (30). The first five preferentially bind IGF-I over IGF-II, while IGFBP-6 has a 100-fold higher affinity for IGF-II compared to IGF-I (31,32). IGFBP-3 is the most abundant IGFBP in serum, is produced primarily from hepatocytes but is also produced from other tissues such as kidney, uterus and placenta (33).

In the circulation, more than 90% of both IGF-I and -II are bound to IGF binding proteins IGFBP3 or IGFBP5 and a glycoprotein called IGFBP6. The rest are bound to the

other IGFBPs and less than 1% circulates as a free form (34). IGF activity is determined by the ratio of free to bound IGF-I, since the bound form does not execute its biological activity (35). IGFBPs compete with IGF-IR and normally have higher binding affinity to IGF-I than IGF-IR does. Therefore, binding of IGFBPs to IGF-I prevents the ligand from interacting with the receptor and, therefore suppresses IGF-I actions. On the other hand, IGFBPs may act as a reservoir of slowly releasing IGF-I, preventing the receptor down regulation by the exposure to high IGF-I levels (36).

Another binding control mechanism is through post-translational modifications (ubiquitination, phosphorylation, etc.) that can alter their ability to bind to IGF-I (36). Post-translational modifications along with the presence of specific proteases that degrade IGFBPs/IGF-I complex have been associated with various types of cancer. There is also a group of cysteine-rich proteins, known as IGFBP-related proteins (IGFBP-rPs), that share important structural similarities with the IGFBPs, but they have low binding affinity to IGFs. It has been proposed that these proteins and the IGFBPs constitute an IGFBP superfamily, however, the functions of the IGFBP-rPs regarding the IGFs actions are yet unclear (37).

IGF receptors and downstream signaling

The IGF receptor (IGF-R) belongs to the family of transmembrane receptor tyrosine kinases and exhibits homology to the insulin receptor (IR). It includes two types: (I) type I, which is the major receptor of IGF-I and (II) type II, to which IGF-II is predominantly attached (38). Type I IGF-IR is composed of 1368 amino acids, consisting of two extracellular α -subunits, the IGF-I binding domain and two transmembrane β -subunits, which contain three tyrosine residues. IGF-I may also be associated with a lower affinity to both type II (IGF-IIR) and IR. The former primarily mediates the internalization of IGF-I as well as metabolic processes while the latter affects cell division (19).

A hybrid IGF-IR/IR receptor consisting of an IR semi-receptor that binds to an IGF-IR semi-receptor has been also described. IGF-I signaling through this hybrid receptor has been implicated in cancer biology (39).

The binding of IGF-I to α -subunits leads to phosphorylation of tyrosine residues which in turn activates a cascade of intracellular reactions leading to mitogenic, anti-apoptotic as well as cell differentiation actions by regulating both normal and abnormal cellular development. More specifically, cytoplasmic molecules

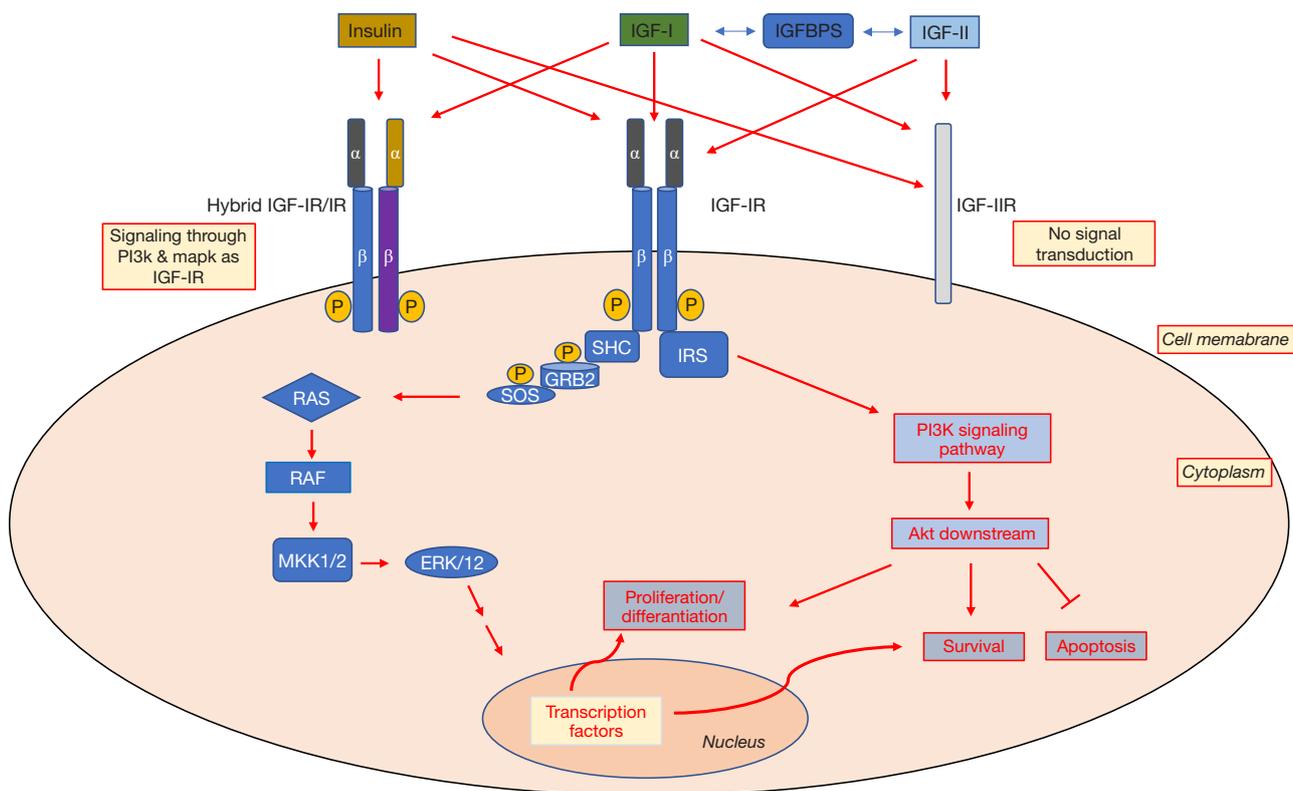


Figure 1 IGF/IGF-IR signaling pathway. The binding of free (not bound to IGFBPs) IGF-I to its receptor phosphorylates the tyrosine residues leading to: (A) IRS/PI3K phosphorylation and subsequent downstream activation of Akt, mediating inhibition of apoptosis and proliferation; (B) Shc/Grb-2/Sos phosphorylation and complex formation, promotes the activation of Ras/Raf/MEK/MAPK cascade, leading to cell proliferation and growth. IGF-I binds to the hybrid IGF-IR/IR receptor activating PI3K and MAPK pathways. IGF-I also binds the IGF-IIR without activating any signaling pathway. Insulin transduces its signal through hybrid IGF-R/IR and IGF-IR, while IGF-II mediates its action through IGF-IR. The arrows indicate an activating effect. ERK, extracellular signal-regulated kinase; Grb2, growth factor receptor-bound protein-2; IGF-I, insulin growth factor-I; IGF-IR, insulin growth factor-I receptor; IGF-IIR, insulin growth factor-II receptor; IR, insulin receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MKK, mitogen-activated protein kinase kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; Src, Src homology and collagen; SOS Son of sevenless.

incorporating insulin receptor substrate proteins (IRS) are activated (40), leading to initiation of two major signaling pathways (Figure 1); the first leads to the activation of 3-phosphatidylinositol kinase (PI3K) involved in cellular processes such as resistance to apoptosis (through protein kinase B or Akt activation), cellular metabolism and growth; the second includes proteins that are involved in the growth factor signaling pathway, such as growth factor receptor-bound protein 2 (Grb-2) and Src homology and Collagen (Shc). The latter is associated with Grb-2 which, through the Grb-SOS complex, promotes activation of Ras-Raf intermediates, which in turn activate extracellular signal-regulated kinases (ERK), leading to cell proliferation and growth. Ras-Raf activates mitogen-activated protein

kinase kinase 1/2 (MKKs), resulting in phosphorylation and activation of extracellular-signal-regulated kinases 1/2 (ERK1/2), which then regulate the action of cellular and nuclear proteins, as well as transcription factors (41).

Expression of the IGF-I receptor seems to be dependent on the cell type, as well as the cellular microenvironment. Recent data reported significant overexpression in various cancer cells (42-44) as well as some autoimmune diseases (8).

The structure of the type II receptor consists of a single polypeptide chain without a kinase domain. It appears to be identical to the cation-independent mannose-6-phosphate receptor, to which it is attached. IGF-IIR does not have a signaling domain and is thought to be involved in the clearance of soluble IGF-II from serum and tissue fluids

through receptor-mediated endocytosis (45).

The physiological action of insulin growth factors

IGFs are involved in many cell processes, including cell differentiation, cell growth, proliferation, and apoptosis (19).

IGF-I plays an essential role in body growth and metabolism, especially during the postnatal life, through the activation of IGF-IR. It has been suggested that serum IGF-I, which is postnatally produced mainly by the liver under GH stimulation though other tissues can serve as potential sources through autocrine and paracrine mechanisms (31). In contrast, serum IGF-I exerts a negative feedback on GH production, either through direct inhibition of the pituitary gland and or indirect stimulation of somatostatin (SST), a known inhibitor of growth hormone releasing hormone (GHRH) (31).

IGF-II is a circulating peptide hormone whose regulation can be under the control of GH (46). IGF-II plays an important role in both developmental and metabolic pathways, especially during the prenatal life. Indeed, IGF-II is preferentially expressed during embryogenesis and fetal development, it stimulates cell growth and proliferation and promotes embryo and fetus growth, through the activation of IGF-IR and IR, in particular the isoform A (IRA), which is predominantly expressed during prenatal life (39,47). IGF-II can also bind to IGF-IIR, which is considered a "scavenger receptor". Indeed, IGF-II binding to IGF-IIR leads to IGF-II degradation by the lysosomes without eliciting proliferation or survival signals (48,49). Overall, IGFs may also play an autocrine or paracrine role by binding to IGF-IR and/or IR on target cells (50).

The interaction of insulin growth factors and immune system

Recent data highlight the interaction between GH, the IGF pathway and the immune system (51). For example, IGF-I levels decrease with age as well as in chronic inflammatory disorders status, resulting in poor immune responses. On the other hand, children with chronic inflammatory diseases exhibit a developmental disorder possibly through IGF-I/GH dysfunction as a result of excessive proinflammatory cytokines (52). IGF pathway has been shown to get involved in the growth of several immune cells including hematopoietic cells, B and T lymphocytes, macrophages and neutrophils (8). In experimental mouse model, hematopoiesis appears to increase after bone marrow

transplantation and co-administration of IGF-I and/or GH (52). In bone marrow, administration of IGF-I promotes the production of mature B cells, while at the level of thymus and spleen it affects the growth of thymic and splenocyte cells, respectively. Depending on their degree of activation, T lymphocytes display differential expression of IGF-I, IGF-II, IGF-IR and IR (8,53). It has been further demonstrated that administration of IGF-I leads to cellular proliferation and chemotaxis possibly through interaction with a network of chemokines, whereas under other conditions it can lead to inhibition of T-cell growth by dampening IL-2 production (53-56). Increased expression of IGF-I is also observed in activated macrophages and neutrophils contributing to innate immune responses (57,58). Taken together, these data highlight an important role of GH/IGF-I pathway in immune functions, though the underlying mechanisms have not been fully elucidated.

The role of insulin growth factors on autoimmune diseases

Autoimmune diseases are a heterogeneous group of disorders with common etiopathogenetic mechanisms, but distinct clinical phenotypes. A genetically determined deregulated immune response in conjunction with hormonal and other environmental factors (e.g., stress, viruses, UV light, medications) leading to chronic inflammatory tissue damage is a well-accepted pathophysiological scenario in these disorders (59). In this context, the contribution of the IGF pathway in immune dysfunction appears to be a new field of investigation and potential target for therapeutic intervention.

RA

RA is a systemic chronic inflammatory disease of unclear etiology. It is characterized by immune activation, leucocyte infiltration and synovial inflammation untimely resulting in joint swelling (60). The cellular composition of the inflamed synovial fluid (SF) includes innate and adaptive immune cells such as T cells, B cells, monocytes and macrophages; moreover, fibroblasts promote chondrocyte catabolism and osteoclastogenesis resulting in articular destruction (61,62). The joint destruction is amplified by elevated levels of cytokines and GHs (63). The proliferation of synoviocytes leads to an increase in metabolic demands, which in turn fuels angiogenesis and expansion of new vessels into cartilage and bone, resulting in matrix degradation (64).

IGF-I is thought to have a key role in the maintenance of the steady-state metabolism of cartilage and several studies suggest that IGF-I stimulates the synthesis and decreases the degradation of proteoglycans in cultured cartilage explants (65,66).

The contribution of IGF/IGFBP axes in RA pathogenesis has been extensively examined giving controversial results. Several studies over the last years reported high IGFBP2, IGFBP3 and IGF-I levels in both plasma and SF of RA patients compared to controls (15,65,67-71), though there are works reporting similar or reduced IGF-I levels in SF (72-74) or reduced IGFBP3 serum levels in RA patients compared to controls (72,75,76). Recently, IGFBP6—a putative novel chemoattracting agent driving T-cell migration from the periphery to the inflamed joints in RA was also found upregulated in synovial RA tissue (77). Upregulation of IGFBPs and IGF-I have been also linked to the presence of proinflammatory cytokines such as interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF α) and C-reactive protein (CRP) (65,68). Of note, an important variant in the promoter of *IGF1* gene has been previously shown to increase RA susceptibility, associated with low IGF-I serum levels and higher disease activity score (DAS) particularly in male individuals non-carrying the wild type 192-bp allele (78).

Additionally, the involvement of IGF-IR in disease pathogenesis has been recently revealed. The main finding is the increased IGF-IR expression in peripheral blood leukocytes which was associated with systemic inflammation (79,80). In contrast, in an arthritis mouse model reduced IGF-IR expression was detected in synovial tissue (ST) and restoration was achieved upon IL-27 and IL-35 treatment (81). Moreover, resistin suppression was associated with down-regulation of IGF-IR expression and a reduction in Akt phosphorylation in human synovial transplants in vivo. The observed high levels of resistin in RA SF were inversely correlated with IGF-I SF levels, while a clear IGF-IR expression was found in the synovium. Abrogation of resistin in the RA synovium using siRNA led to decreased phosphorylation of Akt, suggesting that resistin may activate Akt through IR/IGF-IR, facilitating excessive growth of ST in RA synovium (72).

Another key factor that regulates IGF-IR expression is micro RNA 223 (miR-223) which was found to be overexpressed in RA patients peripheral blood T cells (82-84) and inversely associated with IGF-IR expression (83).

Accumulating data so far, support the role of IGF-I/IGFBPs axes in human cachexia (31,54), a common

manifestation among RA patients characterized by loss of fat-free mass, predominantly skeletal muscle (85). In an RA cohort of sixty patients was observed reduced serum IGF-I/IGFBP1 ratio in patients with cachexia (86). In line with these findings, decreased IGF-I and increased adiponectin serum levels were correlated with higher disease activity and lower muscle mass (87). Interestingly, high-intensity resistance exercise can reduce the RA related cachexia by increasing muscular IGF-I and IGFBP3 expression (88-90).

An interesting new study reported that the thioredoxin domain-containing 5 (TXNDC5) gene is associated with susceptibility to RA and exhibits increased expression in the STs. In vitro experiments showed that TXNDC5 gene expression contributes to abnormal RA synovial fibroblasts (RASFs) proliferation and migration by increasing IGF-I activity through reduction of IGFBP1 levels (91).

Juvenile idiopathic arthritis (JIA)

JIA is a systemic chronic inflammatory disease (92). The term describes a clinically heterogeneous group of arthritides of unknown cause, with onset prior to 16 years of age. Growth retardation is a common feature of JIA (93).

Several studies so far consistently revealed an association between low serum or plasma IGFBP3 and IGF-I levels with the stunted growth observed in the setting of JIA (94-103) (*Table 1*), possibly as a result of excessive inflammatory activity (97,102,104) or increased proteolytic activity of serum gelatinase (94), previously shown to mediate proteolytic degradation of both IGFBP3 and IGF-I (105,106). In contrast, no association between IGF-I levels and cartilage oligomeric matrix protein (COMP) was observed (97,102).

Interestingly, normalization of IGF-I and IGF-IBP3 levels was achieved following treatment with biological agents etanercept and tocilizumab resulting in growth reconstitution in JIA patients (107,108).

Systemic lupus erythematosus (SLE)

SLE is a severe, chronic autoimmune disorder characterized by involvement of multiple organ systems, loss of tolerance to self-antigens and dysregulated interferon responses. The disease can affect many different body systems, including joints, skin, kidneys, blood cells, heart, and lungs (109).

The clinical heterogeneity of SLE is accompanied by complex disturbances in the immune system, with the hallmark of characteristic autoantibodies and an enhanced

Table 1 Differential expression of GH, IGFs and IGFBPs in rheumatoid and juvenile idiopathic arthritis

Study	Patient's and controls age mean or range* (year)	Serum	Plasma	PBMCs	Synovial fluid (SF)	Synovial tissue (ST)
Rheumatoid arthritis						
Alunno <i>et al.</i> , 2017 (77)	57±2.2 vs. NA	NA	NA	NA	↑IGFBP6	↑IGFBP6
Bostöm <i>et al.</i> , 2011 (72)	25–87 vs. 23–88	↓IGFBP3, ↑resistin	NA	NA	↓IGF-I, ↑resistin	NA
Denko <i>et al.</i> , 1996 (73)	NA	NA	NA	NA	↓IGF-I	NA
Erlandsson <i>et al.</i> , (79)	40–64 vs. NA	NA	NA	↑IGF-IR	NA	NA
Fernihough <i>et al.</i> , 1996 (71)	63 vs. 69	NA	↑IGF-I & IGFBP3	NA	NA	NA
Lauberg <i>et al.</i> , 2012 (80)	50.5 vs. 55	NA	NA	↑IGF-IR	NA	NA
Lee <i>et al.</i> , 2006 (75)	30–56 vs. 30–56	↓GH, -IGF-I, ↓IGFBP3, -IGF-II	NA	NA	NA	NA
Lemmey <i>et al.</i> , 2001 (76)	57±2.2 vs. NA	↓IGF-I & IGFBP3	NA	NA	NA	NA
Matsumoto <i>et al.</i> , 1996 (70)	43.6±11.6 vs. 23.4±5.9	NA	NA	NA	↑IGF-I & IGFBP3	NA
Matsumoto <i>et al.</i> , 1998 (69)	20–58 vs. 20–58	NA	NA	NA	↑IGFBP2 & IGFBP3	NA
Matsumoto <i>et al.</i> , 2002 (67)	52 vs. NA	↑IGFBP3	NA	NA	NA	NA
Neidel <i>et al.</i> 2001 (68)	59 vs. 51	NA	↓IGF-II, ↑IGFBP2	NA	NA	NA
Neidel <i>et al.</i> , 1997 (65)	NA	NA	↑IGFBP2 & IGFBP3, -IGF-I & IGF-II	NA	↑IGFBP2 & IGFBP3, -IGF-I & IGF-II	NA
Suzuki <i>et al.</i> , 2015 (15)	58±12.6 vs. 32±6.0	↑IGFBP3	NA	NA	NA	↑IGF-I & IGFBP3
Toussirot <i>et al.</i> , 2005 (74)	47.6±2.1 vs. 44.3±1.7	↑GH, -IGF-I, -IGFBP3	NA	NA	NA	NA
Juvenile idiopathic arthritis						
Bechtold <i>et al.</i> , 2001 (103)	9.7±1.9 vs. 7.8±6.2	NA	↓IGF-I & IGFBP3	NA	NA	NA
Bilginer <i>et al.</i> 2010 (99)	10.5±4.1 vs. NA	↓IGF-I	NA	NA	NA	NA
Bjørnhart <i>et al.</i> , 2009 (97)	6.9 vs. 9.2	↓IGF-I	NA	NA	NA	NA
Bozzola <i>et al.</i> , 2012 (104)	7.6 vs. 8.6	↑IGF-I	NA	NA	NA	NA
Davies <i>et al.</i> 1997 (95)	NA vs. 8.5±2	NA	↓IGF-I	NA	NA	NA
De Benedetti <i>et al.</i> 2001 (96)	2–12 vs. NA	↓IGFBP3	NA	NA	NA	NA
Guszczyn <i>et al.</i> , 2009 (94)	NA	↓IGFBP3 & IGF-I	NA	NA	NA	NA
Lewander <i>et al.</i> , 2017 (102)	12.4 vs. NA	↓IGF-I	NA	NA	NA	NA
Tsatsoulis <i>et al.</i> 1999 (101)	12.4±1.0 vs. 12.6±1.0	NA	↓IGF-I & IGFBP3	NA	NA	NA
Wong <i>et al.</i> , 2008 (100)	6.5 vs. NA	↓IGFBP3	NA	NA	NA	NA

*, mean and range age are expressed in years of patients compared to controls. ↑: increased; ↓: reduced; -: no differences. GH, growth hormone; IGF-I, insulin growth factor 1; IGF2, insulin growth factor 2; IGFBP 2/3, insulin growth factor binding protein 2/3; NA, not available.

type I interferon (IFN) and B-cell activating factor (BAFF)/B lymphocyte stimulator (BlyS) system (110).

The role of IGF/IGFBPs in SLE remains unclear. While no differences in IGF-I/IGFBP3 or free IGF-I serum levels were observed in SLE patients compared to age-matched healthy controls (111,112), IGFBP2 serum levels - the second most prevalent serum IGFBP - have been found to be increased in patients with active SLE compared to healthy controls (113). Another study conducted in a cohort of 86 patients suffering from lupus nephritis (LN), a major complication of SLE, serum IGFBP4 were significantly higher and correlated with chronicity index of renal pathology in LN patients compared to controls (114). Moreover, high mRNA and protein expression of IGF-I and IGFBP2 in kidney sections (115) and increased IGFBP2 serum levels has been detected in a lupus mouse model (116) (Table 2).

Of interest, a genetic variation +3179G/A of the *IGF-1R* gene has been recently shown to increase lupus susceptibility and severity in a Bulgarian population. Upon classification of these patients according to disease activity, significantly increased IGF-I serum levels were detected in very active SLE patients (Systemic Lupus Erythematosus Disease Index SLEDAI score >10) compared to those with mild and moderate disease activity (SLEDAI ≤10) (117).

Systemic sclerosis (SSc)

SSc is a multiorgan disease, characterized by progressive fibrosis of the skin and internal organs (125). Alterations in immune system, vasculature and connective tissue are considered pathogenetic disease hallmarks (126).

IGF-I, among other growth factors, has been implicated in the pathogenesis of several fibrotic disorders (127). While initial reports did not detect any differences in IGF-I levels between SSc patients and controls (121), subsequent studies revealed increased IGF-I (118,119,122) and IGFBP3 serum levels and overexpression of IGF-I mRNA transcripts in skin biopsy of SSc patients (119) (Table 2). Moreover, following disease stratification, patients with diffuse cutaneous systemic sclerosis (dcSSc) displayed higher IGF-I levels compared to those with limited cutaneous systemic sclerosis (lcSSc) (119).

IGF-I/IGFBPs axis has been also implicated in the pathogenesis of pulmonary fibrosis which is the most common cause of SSc-related mortality (128). Increased IGF-I levels have been found in bronchoalveolar lavage fluid in patients with SSc-related pulmonary fibrosis

as well as other forms of pulmonary fibrosis (129). In addition, immunohistochemical overexpression of IGF-II, in explanted lung tissues derived from SSc patients complicated by pulmonary fibrosis has been detected, as well as, increased IGF-II mRNA and protein expression in primary cultured fibroblasts derived from the same SSc lung tissues (120).

Sjögren's syndrome (SS)

SS is a chronic autoimmune disorder that typically affects exocrine glands—mainly labial and lacrimal—leading to complaints of dry mouth and eyes. Given the presence of periepithelial mononuclear cell infiltrates, both in exocrine glands and in other parenchymal organs such as kidney, lung, and liver, the term “autoimmune epithelitis” has been proposed (130).

The presence of IGF-I in the saliva of mammals in association with immunohistochemical evidence of its expression in salivary glands both in human and in experimental models imply a contributory role for this molecule in salivary gland epithelium homeostasis (131). A recent study proposed that pre-treatment of mice with IGF-I before irradiation resulted in reduced DNA damage of salivary glands and alleviation of symptoms associated with radiation treatment (132). Of note, IGF-I expression decreases with age, providing an explanation for the salivary dysfunction related to the atrophic salivary epithelium found in the elderly population (133).

The contribution of the IGF pathway in maintaining both the number of cells of the salivary gland and intercellular junctions, and to ensure the functioning of the salivary glands suggest a possible involvement in the pathogenesis of SS (134). Limited data until today, have revealed reduced immunohistochemical detection of IGF-I receptor in experimental autoimmune sialadenitis (135) and salivary gland biopsies (17) along with increased IGF-I expression in salivary gland biopsies from SS patients compared to controls (124). Furthermore, microarray data on peripheral blood monocytes, showed a clear down-regulation of IGF-IR transcripts in SS patients compared to controls (123).

Conclusions

A growing body of evidence over the last years supports an important role of IGF/IGFBPs axis dysregulation in the pathogenesis of systemic rheumatic diseases. This can

Table 2 Differential expression of IGF & IGFBPs in systemic lupus erythematosus, systemic sclerosis and Sjogren's syndrome

Study	Patient's and controls age mean or range** (year)	Serum	Affected tissue*	Fibroblasts	Plasma	PBMCs
Systemic lupus erythematosus						
Denko & Malemud 2004 (111)	NA	-IGF-I	NA	NA	NA	NA
Ding <i>et al.</i> , 2016 (116)	34.9±1.2 vs. 35.3±1.9	↑IGFBP2	NA	NA	NA	NA
Mok <i>et al.</i> , 2016 (113)	28.7±9.4 vs. NA	↑IGFBP2	NA	NA	NA	NA
Stanilova <i>et al.</i> , 2013 (117)	42.4±13.8 vs. 40.5±18.9	↑IGF-I SLEDAI > 10	NA	NA	NA	NA
Waldron <i>et al.</i> , 2018 (112)	48.55±15.68 vs. 50.17±14.15	-IGF-I & IGFBP3	NA	NA	NA	NA
Wu <i>et al.</i> , 2016 (114)	35.0±1.2 vs. 34.6±1.8	↑IGFBP4	NA	NA	NA	NA
Systemic sclerosis						
Fawzi <i>et al.</i> , 2008 (118)	22.1±14.6 vs. 20.4±2.6	↑IGF-I	↑IGF-I	NA	NA	NA
Hamaguchi <i>et al.</i> , 2008 (119)	46 vs. NA	↑IGF-I & IGFBP3	↑IGF-I mRNA	NA	NA	NA
Hsu & Feghali-Bostwick 2008 (120)	NA	NA	NA	↑IGF-II mRNA	NA	NA
Rothe <i>et al.</i> , 1988 (121)	51 vs. NA	-IGF-I	NA	NA	NA	NA
Winsz-Szczotka <i>et al.</i> , 2016 (122)	53.12±15.56 vs. 50.67±11.2	NA	NA	NA	↑IGF-I	NA
Sjogren's syndrome						
Emamian <i>et al.</i> , 2009 (123)	57±11 vs. NA	NA	NA	NA	NA	↓IGF-IR
Katz <i>et al.</i> , 2003 (17)	68 vs. 24	NA	↓IGF-IR	NA	NA	NA
Markopoulos <i>et al.</i> , 2000 (124)	45.8 vs. NA	NA	↑IGF-I	NA	NA	NA

*Affected tissue: skin in systemic sclerosis, minor salivary glands in Sjogren's syndrome; **mean and range age are expressed in years of patients compared to controls. ↑: increased; ↓: reduced; -: no differences. IGF-I, insulin growth factor 1; IGFBP 2/3/4, insulin growth factor binding protein 2/3/4; IGF-IR, insulin growth factor receptor 1; MSG, minor salivary glands; PBMCs, peripheral blood mononuclear cells; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; NA, not available.

occur either through inhibitory growth signals leading eventually to apoptosis of host cells and generation of aberrant immune responses against self, or promotion of inflammatory processes mediated by inappropriate growth signals to selective immune and non-immune cell populations. Further research is required to fully elucidate the dual role of IGF/IGFBPs system in autoimmune pathology, possibly resulting in novel therapeutic targets.

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Footnote

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