Growth Factors in Inflammatory Bowel Disease

The Actions and Interactions of Growth Hormone and Insulin-Like Growth Factor-I

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Abstract: Multiple growth hormones (GHs) and factors are relevant to inflammatory bowel disease (IBD) due to their trophic effects on epithelial cells to promote mucosal integrity, renewal, and repair, on mesenchymal cells to promote wound healing, and on intestinal immune cells to modulate inflammation. The anabolic effects of GHs and factors outside the intestine are relevant to minimizing nutritional insufficiency, catabolic state, and the inability to maintain body weight due to inflammation-induced malabsorption. GHs and factors can, however, have a dual role, whereby trophic effects can be beneficial but, if excessive, can promote complications including the increased risk of intestinal tumors/adenocarcinoma and fibrosis. This review focuses on GH and insulin-like growth factor (IGF-I), for which evidence suggests such a dual role may exist. The actions of GH and IGF-I on the healthy intestine are compared with effects during intestinal inflammation or associated complications. Interactions between these growth factors and others relevant to IBD are considered. The role of the newly discovered suppressors of cytokine signaling proteins, which may dictate the balance between beneficial and excessive actions of GH and IGF-I, is also addressed.

Key Words: growth hormone, insulin-like growth factor-I, suppressors of cytokine signaling, fibrosis, cell proliferation

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CROHN’S DISEASE AND ULCERATIVE COLITIS

Although the pathogenesis of Crohn’s disease (CD) and ulcerative colitis (UC) have not been fully defined, these two chronic inflammatory diseases of the gastrointestinal tract are thought to involve distinct immunologic mechanisms. Inflammation in UC is generally restricted to the mucosa of the colon and can include epithelial cell destruction. In general, the interest in growth factors and UC or models of mucosal injury focuses on epithelial cell responses to promote mucosal repair. Pertinent to this review, a number of reports suggest that colon adenocarcinoma risk is increased in patients with UC. Therefore, defining whether endogenous or exogenous growth factors alter epithelial cell proliferation or promote cancerous transformation is relevant to UC. Unlike UC, CD primarily affects the ileum and cecum, but also can affect other regions of the gastrointestinal tract. CD can be distinguished from UC by transmural granulomatous inflammation and fibrosis extending beyond the mucosal layer into all submucosal layers. Fibrosis associated with CD is generally considered to be an overzealous, irreversible healing response to chronic inflammation and injury. Fibrosis involves muscularis overgrowth, excessive collagen deposition and mesenchymal cell hyperplasia within the lamina propria, muscularis mucosa, submucosa, muscularis propria, and serosa. Fibrosis and muscularis overgrowth can lead to the development of bowel obstruction, a complication of CD for which surgical intervention currently constitutes the major therapy. High recurrence rates of inflammation and fibrosis in a majority of CD patients contribute to complications including multiple surgeries and short bowel syndrome (SBS). Therefore, in considering the role of growth factors in CD, epithelial responses that influence mucosal repair and mesenchymal responses that dictate normal healing or fibrosis are important.

Growth hormone (GH) has been tested as therapy in IBD patients in several clinical settings. GH therapy counteracts some of the catabolic effects of steroid treatment in children with IBD, including positive changes in bone metabolism, linear growth, and body composition. GH has been tested as therapy in SBS patients in a number of clinical trials. A majority of studies have indicated beneficial anabolic effects in patients with SBS and a reduced need for parenteral nutrition. The effects on nutrient absorption have not been extensively studied, but where they have, different trials have reported varied outcomes. Although GH has received Food and Drug Administration approval for therapy in SBS patients, its use is still controversial. Since a considerable portion of SBS patients have CD, the outcome of GH therapy in SBS patients is relevant to its possible benefits in CD patients. A clinical trial in a small number of patients with active...
CD reported that GH therapy improved the CD activity index (CDAI) and decreased the need for other medications.19

Despite the possible benefits, GH therapy may introduce some risks and complications, either through direct effects or its induction of insulin-like growth factor (IGF-I). Evidence suggests that IGF-I may promote an increased risk of intestinal cancer and fibrosis through excessive trophic drive. High levels of IGF-I in the circulation may increase the risk of colon cancer.20 IGF-I and the type I IGF receptor (IGF-IR) are expressed by colon cancers in situ and by colon cancer cell lines.21–23 Considerable evidence also suggests that local IGF-I acting in a paracrine and/or autocrine manner may be a mediator of excessive wound-healing responses that lead to fibrosis during intestinal inflammation.9,24

The concept that locally produced IGF-I in nonhepatic tissues, extending its plasma half-life. More than 90% of circulating IGF-I and prolong the plasma half-life. More than 90% of circulating IGF-I and IGF-I action by sequestering IGF-I from its receptor. Some membrane or extracellular matrix-associated IGFBPs enhance IGF-I action by serving a growth factor “presentation” function to the IGF-IR, thereby preventing receptor desensitization.

MECHANISMS OF GH AND IGF-I ACTION

The actions of GH can be direct or mediated by the induction of IGF-I. Considerable evidence suggests that the direct effects of GH are mediated by the Janus family kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. GH is part of a cytokine superfamily including pro-inflammatory cytokines such as interferon-γ and interleukin (IL)-6 and anti-inflammatory cytokines such as IL-10, which activate JAK-STAT profiles that are different than those of GH. JAK2 appears to be the major JAK mediating GH signaling, and STAT1, 3, and 5 are the major STATs activated by GH.34,35 GH signaling is arguably best studied in the liver and skeletal muscle. Recent evidence has suggested that Stat5b acts as a key component of GH-induced IGF-I gene transcription in liver since mice lacking Stat5b show diminished growth rates and decreased serum IGF-I levels.36,37 Furthermore, GH does not increase liver IGF-I expression in STAT5b knockout mice.38 In vitro studies in human IM-9 lymphocytes showed
that GH activates Jak2 and STAT5, implicating Jak-2 and STAT-5 as potential downstream mediators of GH signaling in immune cells. Few data exist in epithelial or mesenchymal cells, especially in the intestine. More information is needed to fully define GH action in IBD or the effects of GH therapy.

The binding of IGF-I to the IGF-IR signals are all known growth and differentiative effects of IGF-I. The IGF-IR is a receptor tyrosine kinase expressed in most cell types, excluding hepatocytes and mature B cells. Binding to the IGF-IR initiates multiple signal transduction pathways, including insulin receptor substrate-1 (IRS) Src homology (SH) 2-domain-containing protein (Shc), mitogen-activated protein kinase (MAPK) phosphatidylinositol-3 kinase (PI3K), and Jak5s/Stats in some tissues. Stats could therefore mediate or integrate IGF-I interaction with GH or other cytokines.

**GH/IGF-I in the Normal Intestine**

The GHR is expressed throughout the epithelium and in the lamina propria, muscularis mucosa, submucosa, and muscularis propria, indicating the potential for direct GH action within the bowel. Few in vitro studies have shown the effects of GH on intestinal epithelial cells. One report indicated proliferative effects in the Caco-2 colon cancer cell line, although recent studies in our laboratory have indicated that the mitogenic responses of Caco-2 cells to GH are modest, inconsistent, and very dependent on low cell density. In IEC-6 cells, a nontransformed intestinal epithelial cell line, and in isolated crypts, GH surprisingly attenuated basal DNA synthesis, indicating anti-proliferative actions. These variable responses to GH in intestinal epithelial cell lines are consistent with the variable responses of the intestinal epithelium to GH in vivo. Table 1 summarizes gastrointestinal growth and functional responses to GH or IGF-I in multiple animal models. Potent trophic effects of GH are observed in the intestine of animal models of GH deficiency (hypophysectomized rat) or long-term dramatic GH excess such as GH transgenic mice. The evaluation of shorter term, more therapeutically relevant actions of GH in animals with an intact GH/IGF-I axis has yielded more variable results. Some have not, all studies have indicated that the trophic actions of GH increase mucosal mass in animal models of SBS. In a rat model of total parenteral nutrition (TPN), multiple studies have failed to demonstrate the trophic effects of GH even though GH normalized body weight gain, increased plasma IGF-I levels, and affected some aspects of differentiated function. Recent studies have indicated that during TPN there may be an intestine-specific state of postreceptor resistance to GH. This is relevant to emerging concepts that growth delay in children with IBD may reflect GH resistance. Few studies have demonstrated that GH promotes crypt proliferation, even in models in which GH had some effects on differentiated function and improved body weight gain. Indeed, even in GH transgenic animals only transient effects of GH excess on crypt proliferation were observed at weaning and were not sustained in adult animals despite maintained increases in mucosal mass through adulthood. This contrasts with IGF-I, in which a majority of studies in IGF-I transgenic mice and multiple in vivo models of IGF-I induction, including TPN and resection models, have demonstrated potent trophic actions of IGF-I accompanied by proliferative and anti-apoptotic actions. While these trophic actions of IGF-I may be beneficial to increase the mass of functional intestinal mucosa, they may also increase the risk of intestinal tumors.

Overall, the studies in GH and IGF-I transgenic mice, and GH- and IGF-I-infused animals suggest more complex effects of GH and IGF-I than previously suspected. Despite the long-held view that GH is a trophic hormone and the proliferative effects of which are mediated by IGF-I, evidence in the healthy intestine suggests that IGF-I is a more potent entero-trophic factor than GH. This is found even when GH elevates plasma IGF-I to levels similar to those found in models of IGF-I infusion.

**Benefits and Risks of GH and IGF-I in the Inflamed Intestine**

Evidence in pediatric and adult IBD patients has suggested that the GH/IGF-I axis is functionally impaired during IBD. GH resistance is a complication acquired by many IBD patients, which is characterized by normal GH secretion with impaired induction of GH target genes, including hepatic IGF-I and, consequently, circulating IGF-I. Growth delay is frequently reported in children with IBD, more often in patients with CD than in those with UC. GH is used as therapy for children with CD who exhibit growth delay. Therapeutic GH may be beneficial to overcome or limit GH resistance by increasing ligand and normalizing anabolic effects by increasing circulating GH and IGF-I levels.

In addition to the potential use of GH as therapy for GH resistance and growth delay in pediatric IBD, a clinical trial in a small number of patients with active CD reported that GH therapy improved their CDAI and decreased the need for other medications. Further studies are needed, these results suggest that therapy with GH may be beneficial in CD patients with active inflammation.

Similar to the evidence in IBD patients, a study in rats with experimental colitis induced by trinitrobenzene sulfonic acid showed GH resistance with normal GH plasma concentrations and reduced plasma IGF-I levels. Although undernutrition may be a primary culprit in GH resistance that is associated with human IBD, studies in animal models have implicated proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α as potential mediators of GH resistance independent of undernutrition. Transgenic mice overexpressing IL-6 or TNF-α are growth-impaired with reduced plasma IGF-I levels but normal plasma GH concentra-
The mechanism whereby IL-6 inhibits GH signaling involves IL-6 activation of cytokine-inducible SH2-domain-containing protein (CIS) and a suppressor of cytokine signaling (SOCS)-3 in the liver, both of which are members of the SOCS protein family (Fig. 2). SOCS proteins may act to inhibit GH action and will be discussed in further detail below. In vivo evidence indicates that TNF-α down-regulates hepatic GHR mRNA expression by inhibiting Sp1 and Sp3 transactivators binding to a GHR promoter cis element.71,75

The mechanism of GH action on the intestine during IBD has not been fully defined, however, studies in animal models of intestinal inflammation suggest that GH may act to promote mucosal repair during inflammation. GH transgenic mice have shown improved mucosal repair after acute colitis induced by dextran sodium sulfate (DSS).76 GH transgenic mice also show more rapid but transient increases in crypt cell proliferation than wild-type mice, which is associated with the induction of intestinal trefoil factor,76 a protein that is known to play an important role in the repair and healing of the intestine. Atypical repair was observed in wild-type mice but not in GH transgenic mice, which argues against a tumorigenic role of GH. This is somewhat surprising since GH transgenic mice had elevated circulating levels of IGF-I.76

Few studies have addressed GH action on intestinal collagen-producing mesenchymal cells during intestinal inflammation or injury. Subepithelial myofibroblasts within the lamina propria contribute to wound healing, including increased collagen production and cell proliferation, in response to mucosal damage.7,8 Although these normal responses are essential to promote wound healing, excessive increased collagen deposition and mesenchymal cell hyperplasia can lead to fibrosis. Since fibrosis in CD is transmural, mesenchymal cells residing in each subepithelial layer of the intestinal wall are potential culprits in mediating inflammation-induced intestinal fibrosis. Myofibroblasts are the primary mesenchymal cell type that expresses an active fibrotic phenotype and are thought to be mediators of intestinal fibrosis.7,8 Preliminary studies in cultured intestinal myofibroblasts have shown increased type I collagen accumulation when treated with GH.77 This indicates responsiveness to GH and raises the possibility that GH therapy in IBD patients could increase collagen deposition or fibrosis. However, in vitro studies on mesenchymal cells may not adequately reflect in vivo IBD, and, for that reason, further studies in animal models are necessary. Our laboratory is currently examining the effects of GH in the peptidoglycan-polysaccharide (PG-PS) rat model, which is a chronic T-cell-mediated animal model of intestinal inflammation and fibrosis. Preliminary data have suggested that GH actually reduces rather than increases the severity of fibrosis in the cecum of PG-PS-treated rats compared with vehicle controls.78 GH does not further increase local IGF-I expression, which is induced in the PG-PS model and all animal models of IBD tested and in CD.9,79–82 These results indicate that GH may not exacerbate fibrosis during chronic inflammation despite in vitro effects to increase collagen production by intestinal mesenchymal cells. However, more work is needed to determine the

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mechanism of GH action on the intestinal mesenchyme during inflammation in vivo.

Available evidence has suggested that the local expression of IGF-I occurs primarily in mesenchymal cells of the lamina propria of the normal intestine. Mesenchyme-derived IGF has displayed paracrine actions by increasing epithelial cell proliferation and by having synergistic proliferative effects with other growth factors such as epidermal growth factor. IGF-I also has autocrine actions that increase the proliferation and growth of mesenchymal cells. Collectively, these results suggest that IGF-I derived from intestinal mesenchymal cells regulates the growth and function of neighboring epithelial cells, as well as mesenchymal cells themselves. Further support for this hypothesis comes from observations that levels of local IGF-I mRNA expression correlate with bowel growth during periods of altered nutrient status and disease.

While having potentially beneficial effects to promote mucosal repair and growth, other evidence suggests that increased local IGF-I expression may lead to intestinal fibrosis in IBD. Increased IGF-I expression is localized to myofibroblasts and smooth muscle cells at sites of increased collagen mRNA expression and fibrosis in patients with CD and in animal models of chronic intestinal inflammation. IGF-I stimulates collagen protein synthesis, and the proliferation of enteric smooth muscle cells and intestinal myofibroblasts in vitro and in vivo. IGF-I interacts with other cytokines and growth factors leading to a profibrotic state in the intestine. IGF-I and transforming growth factor (TGF)-β1 are thought to be involved in extracellular matrix remodeling in IBD. Both TGF-β1 and IGF-I stimulate the migration of colonic myofibroblasts, which is a required mechanism for wound healing and could lead to fibrosis through the migration of fibrogenic myofibroblasts into subepithelial layers. Endogenous TGF-β1 regulates the autocrine IGF-I-induced growth of intestinal muscle cells by mediating the production of IGFBP-3 and IGFBP-5. The treatment of intestinal fibroblasts with TGF-β1 induces IGF-I expression in these cells, and IGF-I stimulates the growth of CCD-18Co cells that have first been activated to a fibrogenic myofibroblast phenotype by TGF-β1. There is also evidence that IGF-I interacts with TNF-α. Preliminary in vitro data have indicated that IGF-I interacts with TNF-α to increase intestinal myofibroblast proliferation and collagen deposition. These data indicate that locally expressed, mesenchymal cell-derived IGF-I may mediate inflammation-induced intestinal fibrosis in a paracrine and/or autocrine manner, and may act with other cytokines and growth factors that are up-regulated during inflammation to exacerbate fibrosis.

Overall, the information on GH and IGF-I in the healthy and inflamed intestine indicates divergent, context-dependent roles and questions the traditional view that IGF-I mediates GH action. In the healthy intestine, IGF-I is a much more potent mitogen for intestinal epithelial cells. While both GH and IGF-I have been implicated as risk factors for the development of colorectal cancer, it is noteworthy that increased risk occurs with elevated IGF-I within the normal range, while increased risk due to elevated GH is most commonly associated with excessive GH in situations such as acromegaly. Intestinal inflammation appears to promote systemic GH resistance, which impacts the anabolic and growth-promoting effects of GH (Fig. 2), but in this setting GH promotes normal mucosal repair and transient increases in cell proliferation in the intestine (Fig. 3). Whether these beneficial effects relate to circulating IGF-I remains to be established. Despite the possible beneficial role of circulating IGF-I as a mediator of GH-induced mucosal repair, considerable evidence points to elevated local IGF-I expression as a mediator of fibrosis in CD. Fully defining the role of GH and IGF-I in IBD needs to take into account circulating as well as local levels of IGF-I expression. In addition, increasing and recent evidence suggests that the SOCS family of proteins may play a role in the divergent and beneficial or detrimental effects of GH and IGF-I.

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SOCS: MODULATORS OF GH AND IGF ACTION

As noted above and as their name suggests, SOCSs are intracellular signaling molecules that are induced by cytokines and act in a negative feedback manner to limit the magnitude or duration of cytokine action. The SOCS family consists of eight members (SOCS 1–7 and CIS), of which SOCS 1 to 3 and CIS are the best characterized. SOCS proteins share common structural motifs including a central SH2-domain and a carboxy-terminal SOCS box.\textsuperscript{35-37} Cytokine induction of SOCS proteins occurs subsequent to their activation of JAK-STAT, with STATs proposed as direct mediators of SOCS induction. SOCS proteins attenuate cytokine action by binding directly to cytokine receptors or by associating with JAKs and inhibiting downstream signaling or targeting bound signaling proteins for proteasomal degradation.\textsuperscript{96}

Genetically modified mice have been created to clarify the physiologic roles of the four best-characterized SOCS proteins. The deletion of these SOCS genes has indicated that specific SOCS may be associated with modulating the signaling of certain cytokines or growth factors. For a comprehensive and detailed review of SOCS and their relevance to the gastrointestinal tract, see Greenhalgh et al.\textsuperscript{98} SOCS-1 knockout animals are born healthy but die before weaning with severe inflammatory responses, including lymphopenia, activation of peripheral T cells, necrosis of the liver, and infiltration of macrophages in most organs. These defects occur mainly as a result of deregulated interferon-γ signaling.\textsuperscript{99} Mice that are deficient in genes coding for SOCS-2 (SOCS-2\textsuperscript{−/−}) are larger than their wild-type littermates, and their phenotype indicates enhanced GH and/or IGF action.\textsuperscript{100} While the deletion of both SOCS-3 alleles in mice is embryonic, lethal but targeted deletion in immune cells or hepatocytes indicate that SOCS-3 is a major modulator of IL-6 action.\textsuperscript{101-103} The phenotype in mice lacking CIS has not been fully characterized.

SOCS-1, SOCS-2, SOCS-3, and CIS are each expressed in the healthy intestine\textsuperscript{45,98,104} and modulate the actions of virtually every cytokine implicated in the pathophysiology of IBD.\textsuperscript{99,105,106} This article focuses on SOCS-2 and SOCS-3 because the available data indicate that SOCS-2 plays a role in GH and/or IGF-I signaling,\textsuperscript{100,107} and that SOCS-3 functions as a negative regulator of inflammatory cytokines relevant to IBD and may also contribute to the hepatic and systemic GH resistance associated with IBD.\textsuperscript{74,99,104,108}

SOCS-2

SOCS-2 is up-regulated in the intestine in vivo by GH but not by IGF-I.\textsuperscript{45,98} It is therefore possible that SOCS-2, which is induced by GH, may limit the actions of GH and possibly IGF-I. Data from SOCS-2\textsuperscript{−/−} mice provide evidence that SOCS-2 has a particular role in limiting the trophic and/or fibrogenic actions of GH or IGF-I in a normal setting (Fig. 1). SOCS-2\textsuperscript{−/−} mice are significantly larger than their wild-type littermates, show overgrowth of certain organs, including the intestine,\textsuperscript{45} and have increased expression of several hepatic genes known to be regulated by GH.\textsuperscript{100} Preliminary data suggest that intestinal myofibroblasts isolated from SOCS-2\textsuperscript{−/−} mice show increased cell proliferation induced by IGF-I compared with intestinal myofibroblasts isolated from wild-type mice.\textsuperscript{77} Evidence that SOCS-2 may play a role in modulating collagen deposition was first indicated by findings that SOCS-2\textsuperscript{−/−} mice have increased collagen in their skin.\textsuperscript{100} In the recovery phase following DSS-induced acute intestinal inflammation, preliminary data indicate that SOCS-2\textsuperscript{−/−} mice show increased intestinal fibrosis and collagen protein accumulation compared with wild-type mice.\textsuperscript{109} Together, these findings suggest that SOCS-2, induced by GH or other cytokines, may prevent excessive cell proliferation and collagen deposition, which could otherwise lead to aberrant growth or fibrosis and instead allows tissues to undergo normal growth and wound repair (Fig. 1).
Evidence that SOCS-2 could play a role in limiting the proliferation of intestinal epithelial cells or promoting tumor suppression comes from studies in a colon cancer cell line as well as those in intestinal crypts and myofibroblasts isolated from SOCS-2 

mice. The overexpression of SOCS-2 in Caco-2 colon cancer cells inhibits cell proliferation and promotes differentiation, whereas SOCS-2 

intestinal crypts show enhanced cell proliferation in response to GH or IGF-I. These findings suggest that SOCS-2 attenuates GH and IGF-I-mediated cell proliferation in the intestine (Fig. 1).\textsuperscript{45} The preliminary study noted earlier that using intestinal myofibroblasts isolated from SOCS-2 

mice provides additional evidence that SOCS-2 may lead to an inhibition of cell proliferation.\textsuperscript{77} Other evidence that SOCS-2 may suppress tumor growth is derived from studies in chronic myeloid leukemia (CML) patients and cell lines associated with this neoplastic disease of hematopoietic stem cells. The dysregulation of the tyrosine kinase Bcr-abl is critical to the pathogenesis of CML. SOCS-2 is up-regulated in Bcr-abl-positive cells and in patients with CML who are in blast crisis. Ectopic overexpression of SOCS-2 in Bcr-abl-positive cells leads to a suppression of cell growth and to increased sensitivity to STI571-induced apoptosis.\textsuperscript{110} Additional studies are required to determine whether SOCS-2 is critical for the suppression of intestinal tumor growth.

SOCS-3

Evidence suggests that SOCS-3 is induced by proinflammatory cytokines, such as IL-6, during inflammation to limit further damage and lead to beneficial effects such as mucosal repair.\textsuperscript{104} SOCS-3 is expressed in naïve and activated T cells, particularly T-helper type 2 cells, and in macrophages, suggesting a role for SOCS-3 in modulating inflammatory responses.\textsuperscript{103,111–113} Unlike IL-6, IL-10 has potent anti-inflammatory effects. The actions of both cytokines are mediated by STAT3. Until recently, it was unclear how these two cytokines could function using STAT3 while simultaneously having opposing actions. Yasukawa et al\textsuperscript{103} found that SOCS-3 selectively blocks IL-6 action without interfering with IL-10 action, demonstrating different mechanisms of action. This finding strongly indicates a role for SOCS-3 in the balance between pro-inflammatory and anti-inflammatory responses. Consistent with these results, IL-6 is highly expressed in the intestine during IBD, and SOCS-3 is up-regulated in inflamed colons from patients with CD and UC, as well as in a number of animal models of experimental colitis.\textsuperscript{104,108,114} Furthermore, mice treated with DSS to induce acute colitis have shown increased SOCS-3 mRNA expression during the recovery phase following the withdrawal of DSS, suggesting that SOCS-3 may play a role in mucosal repair.\textsuperscript{104} The dysregulation of SOCS-3 expression appears to increase susceptibility to mucosal injury, as a dominant negative form of SOCS-3/SOCS-1 in mice caused more severe disease following DSS-induced colitis.\textsuperscript{104}

While there is as yet little evidence that SOCS-3 modulates GH action in the intestine,\textsuperscript{77} SOCS-3 mRNA is rapidly and transiently induced by GH in the liver and in hepatocytes in vitro.\textsuperscript{115–118} The overexpression of SOCS-3 leads to a reduction in GH-induced STAT5 activation while the attenuation of JAK2 phosphorylation is controversial.\textsuperscript{119,120} More recent studies in adipocytes and pancreatic B cells provide additional evidence that downstream signaling molecules induced by GH are inhibited by SOCS-3. The overexpression of SOCS-3 in adipocytes impairs GH signaling.\textsuperscript{121} In pancreatic B-cells or insulin-producing INS-1 cells, GH induces SOCS-3, and SOCS-3 inhibits GH-induced STAT5 and STAT3 DNA-binding activity, cell proliferation, and insulin induction.\textsuperscript{122,123} How SOCS-3 impacts on GH action in the intestine during IBD is unknown, but it is tempting to speculate that SOCS-3 may limit the fibrogenic actions of GH or its ability to induce IGF-I, thereby preventing fibrogenic actions of GH. It may also limit the proliferative effects of GH or IGF-I on the intestinal epithelium in magnitude or duration, favoring normal repair rather than excessive proliferation (Fig. 3).

The GH resistance associated with acute and chronic inflammatory diseases is evidenced by normal GH secretion with reduced activation of GH-targeted genes such as IGF-I. SOCS-3 may contribute to this condition by inhibiting GH signaling in the liver (Fig. 2). IL-6 induces CIS and SOCS-3, which inhibit the GH activation of STAT5b, a transcription factor that is required for increased IGF-I expression.\textsuperscript{74} In this setting, GH therapy may have beneficial effects by overcoming the hepatic GH resistance that is mediated by SOCS-3.

At present, there is little evidence that SOCS-3 leads to tumor suppression in the intestine. However, a recent study in the lung found that SOCS-3 inhibits cell proliferation and induces apoptosis, promoting tumor suppression. SOCS-3 is silenced by promoter hypermethylation in human lung cancer cell lines and primary lung cancer tissue. The restoration of SOCS-3 to these cells or tissues induces apoptosis and suppresses cell growth.\textsuperscript{124} Future studies targeting intestinal epithelial cells and mesenchymal cells will be of interest to determine whether SOCS-3 plays a role in GH resistance and/or tumor suppression in the intestine or dictates the balance between the beneficial mucosal repair induced by GH or IGF-I and the excessive effects that could favor tumorigenesis.

CONCLUSIONS AND FUTURE STUDIES

GH has beneficial actions when used as clinical therapy in IBD patients with growth delay, SBS, and active CD. GH therapy could cause complications through the induction of IGF-I, which may increase intestinal cancer risk and/or fibrosis, although the available evidence in animal models of IBD argues against these effects.\textsuperscript{76,78} Further study is needed to fully determine the role of GH, GH-induced IGF-I, and local IGF-I in intestinal fibrosis and tumorigenesis. The direct testing of GH in CD patients and animal models of chronic IBD,
especially CD, is required to determine the benefits and potential risks of GH therapy in IBD. Studies using anti-IGF-I antibodies or soluble IGF-IR as therapy in animal models of IBD will determine the role that IGF-I plays in intestinal fibrosis and tumorigenesis. A constitutive or inducible mesenchymal cell-specific deletion of IGF-I would help to determine the specific effect of locally expressed mesenchymal cell-derived IGF-I compared with that of circulating IGF-I. This would be possible using a constitutive or inducible mesenchyme Cre-recombinase-mediated specific knockout in Lox-P/IGF-I mice. These future experiments will provide key information about the benefits and/or risks of endogenous GH and IGF-I or therapeutic GH, and their roles in intestinal fibrosis and tumorigenesis.

As we gain further understanding about SOCS proteins, it is apparent that they play a critical role in maintaining normal responses and preventing excessive ones. SOCS-2 and SOCS-3 may dictate the balance between the beneficial and excessive actions of GH and IGF-I as well as their interactions with proinflammatory and antiinflammatory cytokines. Additional studies may provide new insights into strategies or therapies using SOCS to limit inflammation, fibrosis, or excessive cell proliferation.

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