Abstract. Crohn’s disease and ulcerative colitis are inflammatory diseases of the gastrointestinal tract characterized by chronic relapsing inflammation and catabolism. Growth hormone/insulin-like growth factor-I axis is important in inflammatory bowel disease, because of the effects on epithelial cell kinetics, collagen deposition and immunomodulation. The potential of growth hormone as a therapeutic option in inflammatory bowel disease has been proven in various clinical settings. Acquired growth hormone resistance in inflammatory bowel disease seems to be mediated by a combination of undernutrition and active inflammation. In particular, proinflammatory cytokines, such as TNF-α and interleukin-6, have been implicated as potential mediators of growth hormone resistance. The introduction of anti-TNF-α monoclonal antibodies has proven very efficacious in patients with inflammatory bowel disease. By reducing cytokines levels in inflammatory cells of intestinal mucosa, infliximab could interfere with cytokine-induced growth hormone resistance. Recent in vivo data have shown that acquired growth hormone resistance in patients with inflammatory bowel disease may be reversed after the administration of anti-TNF-α therapy.

Key Words: Inflammatory bowel disease, Growth hormone/insulin-like growth factor-I axis, Infliximab.

Introduction

Crohn’s disease (CD) and ulcerative colitis (UC), the two most common forms of inflammatory bowel disease (IBD), are inflammatory diseases of the gastrointestinal tract characterized by chronic relapsing inflammation and catabolism. The underlying pathogenetic mechanisms have not been fully defined, but IBD is thought to result from inappropriate activation of the mucosal immune system driven by the presence of normal luminal flora or other environmental factors in genetic susceptible individuals. CD can affect all the gastrointestinal tract and it is characterized by transmural granulomatous inflammation and fibrosis which involves muscularis overgrowth, excessive collagen deposition and mesenchymal cell hyperplasia that can lead to the development of bowel obstruction. High recurrence rates of inflammation and fibrosis contribute to CD complications, including multiple surgeries and short bowel syndrome (SBS). On the other hand, inflammation in UC is generally limited to the colonic mucosa, involving epithelial cell destruction.

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) are relevant to IBD, because of their trophic effects on epithelial cells (e.g. mucosal integrity, renewal, repair), mesenchymal cells (e.g. wound healing) and intestinal immune cells (e.g. modulation of inflammation). The anabolic effect mediated through the GH/IGF-I axis is important to minimize nutritional insufficiency and wasting due to inflammation-induced malabsorption. On the other hand the trophic effect of the GH/IGF-I axis, if excessive, may promote some unwanted complications, such as fibrosis and increased risk of intestinal carcinoma.

The potential of GH as a therapeutic option in IBD has been proven in various clinical settings. GH therapy has been proposed in children with IBD to balance the catabolic effects of corticosteroids. GH has received Food and Drug Administration (FDA) approval for therapy in SBS, because its beneficial anabolic effects and the reduced need for parenteral nutrition. GH therapy has been tested in a small number of active CD patients, improving the disease activity index and decreasing the need for other medications. The potential interest of growth factors in UC focuses on epithelial cell response...
to promote mucosal repair. Because of the increased colon adenocarcinoma risk in patients with UC, defining growth factors that may alter epithelial cell kinetics could be of relevant importance. IGF-I may, in fact, increase the risk of bowel cancer and fibrosis, as demonstrated by in vivo and in vitro studies.

Growth failure in children and weight loss and catabolism in adults are frequent features associated with IBD, attributed to reduced food intake, malabsorption, protein loss and increased energy expenditure. Although IBD-associated malnutrition is considered the main source of these complications, recent evidence in IBD animal models suggests a direct adverse effect of systemic inflammation on the GH/IGF-I axis. Acquired GH resistance in IBD seems to be mediated by a combination of undernutrition and active inflammation. In particular, proinflammatory cytokines (e.g. IL-6, TNF-alpha) have been implicated as potential mediators of GH resistance.

The GH/IGF-I Axis in the Normal and the Inflamed Intestine

GH, released from the anterior pituitary gland, enters the circulation and binds to the GH receptor (GHR) in the liver, in the intestine and other tissues, stimulating the production of IGF-I. Six IGF binding proteins (IGFBPs1-6) can prolong IGF-I action by extending its plasma half-life. More than 90% of circulating IGF-I forms an high-molecular-weight complex with IGFBP3 and an acid labile subunit (ASL) that cannot cross capillary membranes, and may serve as reservoir for circulating IGF-I. GH/IGF-I axis is considered of fundamental importance in somatic growth during postnatal development and in regulating nitrogen balance and tissue growth during adulthood. The action of GH may be direct or indirect, mediated by the induction of IGF-I. The direct effect of GH is mediated by the Janus family kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. JAK2 appears to be the major JAK mediating GH signalling and STAT5b seems to be a key component of GH-induced IGF-I gene transcription. Mice lacking STAT5b show diminished growth rates and decreased serum IGF-I levels. The signals generated by the binding of IGF-I to its receptors have well known growth and differentiative effects. The IGF-I receptor is a tyrosine kinase that promotes multiple signal transduction pathways (e.g. MAPK/PI3K, JAK/STAT) in various tissues. Among them, JAK/STAT pathway could mediate IGF-I interaction with GH. The GH receptor is expressed throughout the epithelium and the lamina propria, muscularis mucosa, submucosa and muscularis propria, indicating the potential for direct GH action within the bowel. GH and IGF-I together are considered to be key determinants to promote wound healing and growth of the intestine by increasing cell proliferation and collagen deposition. It has been reported the proliferative effects of GH in the Caco-2 colon cancer cell line, although recent studies have indicated that the mitogenic responses of Caco-2 cells to GH are modest and very dependent on low cell density. Some studies have indicated that the trophic actions of GH increases mucosal mass in animal models of SBS. Conversely, in GH transgenic animals, only transient effects of GH excess on crypt proliferation were observed at weaning and were not sustained in adult animals. These variable responses to GH in intestinal epithelial cells are consistent with the variable responses to GH in vivo. Indeed, a majority of studies in IGF-I induction have demonstrated potent trophic effects of IGF-I by proliferative and anti-apoptotic actions. Evidence in the healthy intestine suggests that IGF-I is a more potent enterotrophic factor than GH.

GH resistance is a complication acquired by many IBD patients. This is characterized by normal GH secretion with impaired induction of GH target genes that includes the reduction of hepatic and circulating IGF-I. Children with IBD may frequently present growth delay and GH therapy could be useful to limit GH resistance through the increase of circulating GH/IGF-I levels and the normalization of anabolic effects.

Therapeutic GH may be beneficial to overcome or limit GH resistance by increasing GH and IGF-I levels. Slonim et al, in a clinical trial on a small number of patients with active CD, reported that GH therapy improved their CDAI and decreased the need for other medications. Studies in animal models of intestinal inflammation suggest that GH may promote mucosal repair during inflammation. After
acute colitis induced by dextran sodium sulfate (DSS), GH transgenic mice have shown a more rapid but transient increases in crypt cell proliferation than wild-tipe mice, associated with the induction of intestinal trefoil factor23. The GH action on intestinal collagen-producing mesenchymal cells during intestinal inflammation is uncertain. Myofibroblasts are the primary mesenchymal cell type that express an active fibrotic phenotype and are thought to be mediators of intestinal fibrosis24. Preliminary studies in cultured intestinal myofibroblasts have shown increased type I collagen accumulation when treated with GH. Conversely, in the peptidoglycan-polysaccharide (PG-PS) rat model, which is a chronic T-cell-mediated animal model of intestinal inflammation and fibrosis, GH reduces rather than increases the severity of fibrosis25. These results indicate that GH may not exacerbate fibrosis during chronic inflammation despite in vitro effects. However further studies in animal models are necessary to establish the in vivo role of GH in IBD.

IGF-I stimulates collagen protein synthesis26, and the proliferation of enteric smooth cells and intestinal myofibroblasts in vivo and in vitro6. Available evidences have suggested that locally expressed, mesenchymal cell-derived IGF-I acts in a paracrine manner by increasing epithelial cell proliferation and by having synergistic effects with other growth factors such as epidermal growth factor27 and cytokines. IGF-I and transforming growth factor (TGF)-β1 are thought to be involved in extracellular matrix remodelling in IBD by stimulating the migration of fibrogenic myofibroblasts into subepithelial layers28. Furthermore TGF-β1 mediates the production of IGFBP-3 and IGFBP-5 and, in this way, regulates the autocrine IGF-I-induced growth of intestinal muscle cells. There is also evidence that IGF-I interacts with TNF-α to increase proliferation and collagen deposition. IGF-I also has autocrine actions that increases the proliferation and growth of mesenchymal cells27. 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.

**Proinflammatory Cytokines and GH Resistance in IBD**

Although undernutrition may be the main cause of GH resistance, studies in animal models have invoked proinflammatory cytokines, such as IL-6 and tumor necrosis factor (TNF)-α, as potential and independent mediators of GH resistance29. In particular, IL-6 induces CIS and SOCS-3, which inhibit the GH activation of STATb5, a transcription factor for increased IGF-I expression. The SOCS family consists of eight proteins (SOCS 1-7 and CIS) and acts as intracellular signalling molecules. Furthermore, TNF-α down-regulates hepatic GHR mRNA expression by inhibiting Sp1 and Sp3 transactivators binding to a GHR promoter cis element6.

Recent in vivo data have shown that GH resistance in IBD patients may be reversed after the administration of anti-TNF-α therapy30-32. The introduction of anti-TNF-α monoclonal antibodies (infliximab) has proven very efficacious in patients with IBD33-35. In particular by reducing cytokines levels in inflammatory cells of intestinal mucosa, infliximab could interfere with cytokine-induced GH resistance. Preliminary data30 have shown that in patients with active Crohn’s disease the systemic inflammatory condition is associated with a degree of impaired GH response to GHRH plus arginine and low serum IGF-I basal level, possibly induced by inflammatory cytokines. The administration of infliximab seems to acutely restore the GH/IGF-I axis at both central and peripheral levels. In another study it has been reported that infliximab induction treatment in IBD reverses GH resistance through the suppression of systemic inflammation. The restored GH/IGF-I axis is impaired again following the prolonged interval between maintenance infusions, possibly because of the subclinical reactivation of the inflammatory process32.

**References**


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