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Insulin-like Growth Factors in the Gastrointestinal Tract and Liver

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INSULIN-LIKE GROWTH FACTORS

Overview and Discovery of Insulin-Like Growth Factors

The IGF family includes three structurally related ligands: insulin, IGF-I, and IGF-II and two high-affinity cell-surface receptors: the IGF-I receptor (IGF-IR) and the IGF-II receptor (IGF-IIR). Although the insulin receptor (IR) shares significant, ~70%, sequence homology with the IGF-I receptor it possesses a distinct ligand affinity profile. The IGF binding proteins (IGFBP1–6) are important physiologic regulators of the interaction of IGFs with their receptors within the gastrointestinal tract and liver. Growth hormone (GH) is structurally unrelated to IGFs, but its actions are mediated primarily through regulation of IGF-I synthesis and secretion by the liver; hence, GH and its biology are intimately intertwined with IGF-I and are referenced in this chapter.

The IGF system functions as a leading endocrine, paracrine, and autocrine regulatory axis for cellular proliferation, survival, and apoptosis in the gastrointestinal tract. In addition, it has general activities relating to energy metabolism, body size, carcinogenesis, and various organ specific functions. A number of comprehensive reviews have been written (1–9).

Insulin-Like Growth Factor Genes and Proteins in the Gastrointestinal Tract and Liver

IGF-I and IGF-II are two closely related members of the insulin superfamily of peptide hormones. IGF-I and IGF-II are 67% identical, single-polypeptide chains that share ~40% amino acid identity with insulin. Unlike insulin, IGFs are not produced and stored solely in β-cells of the pancreatic islets as is insulin. They are synthesized and secreted by many cells in the body, including cells of the gastrointestinal tract and liver, in a highly regulated manner.

The IGF-I gene is located on human chromosome 12q22–q23. The genomic sequence is large, spanning more than 80 kB DNA, including 6 exons (10). At least 4 transcriptional start sites have been identified, and IGF-I mRNA species range from about 1.0 to 8.0 kB. Complex, tissue-specific alternate splicing patterns have been observed, but the biological

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significance of these variants has not been clearly delineated for gastrointestinal tissues (11). For human pro-IGF-I, two primary translation products exist, IGF-IEa and IGF-IEb. The most commonly recognized mature IGF-I. IGF-IEa, is a 70-amino-acid, secreted protein. The existance of a putative peptide derived from alternative splicing which yields the IGF-IEc variant, mechanogrowth factor (MGF), remains speculative (12). However, evidence suggests MGF plays a role in pathophysiologic response of the gastrointestinal smooth muscle to inflammation and injury (13).

The majority of IGF-I in the peripheral circulation is synthesized in the liver under the control of GH and circulates bound to IGFBPs, primarily IGFBP-3 and the acid-labile subunit (ALS) as a ternary complex. In this context, IGF-I is an endocrine hormone growth factor that stimulates somatic growth and exerts feedback to the pituitary to down-regulate GH synthesis. Most growth-stimulating activities of GH can be mimicked by IGF-I. Peripheral tissues in the gastrointestinal tract are also abundant sources of IGF-I, particularly intestinal smooth muscle, that acts in an autocrine and paracrine fashion to regulate cell growth and survival. While GH regulates IGF production in the liver and in other tissues as well under normal circumstances (see later), in disease states, e.g. malnutrition and Crohn's disease, a relative GH-insensitive state exists whereby the stimulatory effect of GH on IGF-I expression and secretion are markedly reduced and IGF-I expression is regulated by other factors. IGF-I binds to the IGF-IR with high affinity and to the IGF-IIR with lower affinity.

The human IGF-II gene is located on chromosome 11p15.5. Like the IGF-I precursor, the IGF-II precursor is large, and multiple splice variants have been described, many of which are developmentally regulated and contain gut-specific promoters (14). A pro-IGF-II–containing carboxy-terminal precursor sequence is secreted from cells before processing to the mature 67-amino-acid protein (5). The IGF-II gene is relatively unique in that it is "imprinted" in 90% of humans, meaning that normally one allele is silenced on the basis of parental origin. When maternal IGF-II silencing is lost (LOI), biallelic IGF-II expression correlates strongly with the hypomethylation of a differentially methylated region (DMR) near its promoter and results in increased IGF-II levels. IGF-II levels resulting from LOI are increased and are associated with an increased risk for a variety of cancers including colorectal cancer (15) More recently other mechanisms responsible for elevated levels of IGF-II in colorectal cancer have been identified including microsatellite instability (16). IGF-II binds to both IGF-1R and IGF-IIR with high affinity.

Insulin-Like Growth Factor Receptor Genes and Proteins

The IGF-I receptor (IGF-IR) gene is located on human chromosome 15q26.3 and is 70% identical to the insulin receptor gene (17). The protein is synthesized as a single polypeptide chain that is cleaved by proteolysis at a tetrabasic amino acid site resulting in α and β subunits. These subunits associate by disulfide bridging into α and β heterodimers that further associate by disulfide bridging forming the mature heterotetrameric $\alpha_2\beta_2$ receptors. Structurally, this overall configuration is identical to the insulin receptor; in fact, hybrid IGF-IR and insulin receptors are well recognized (18). Most biological activities of IGF-I and IGF-II in the gastrointestinal tract and liver are mediated by the IGF-IR.

IGF-I binding results in autophosphorylation of specific cytosolic tyrosine residues within the IGF-IR receptor, activation of its intrinsic tyrosine kinase activity, and phosphorylation of intracellular substrates (Fig. 1). Insulin receptor substrate 1 (IRS-1), a 185-kDa intracellular signaling protein with multiple phosphorylation sites and SH domains permitting docking of multiple intracellular signaling molecules is a key early mediator of IGF-IR function (19). The result of IRS-1 phosphorylation is activation of a variety of signaling cascades, including the Ras-Erk1/2 and phosphoinosotide-3 kinase (PI-3K) pathways. The IGF-IR also activates the heterotrimeric G-protein, G_{i2}, that is coupled to

activation of the Erk1/2 pathway (20). In intestinal smooth muscle, the intensity and duration of IGF-I stimulated IGF-IR activity is positively regulated by ligand occupancy of αVβ3 integrin by the resultant temporally regulated translocation of SH2 domain-containing tyrosine phosphatase-2 from αVβ3 integrin to the IGF-I receptor (21). Activation of IGF-IR regulates cellular proliferation and survival, key regulatory activities of IGFs in the gastrointestinal tract.

The IGF-IIR, also referred to as the cation-independent mannose-6 phosphate receptor, bears no structural homology with the IR or IGF-IR (9). It is located on human chromosome 6q26. The IGF-IIR receptor is a single, transmembrane polypeptide that binds IGF-II with a greatly reduced affinity for IGF-I and insulin. It has 15 cysteine-laden, contiguous, extracellular repeats and a short intracellular sequence with no recognizable signaling motifs (4). While the function of IGF-II signaling is controversial, and most experts believe it down-modulates IGF-II activity by regulating its endocytosis and intracellular degradation by targeting the proteins to the lysosome. This is relevant to the gastrointestinal tract and is consistent with data showing that IGF-IIR is a tumor-suppressor gene, acting as a “sink” or reservoir for IGF-II and consistent with the effects of LOI of IGF-II in colorectal cancer(6, 15, 16, 22).

Insulin-Like Growth Factor Binding Protein Gene and Protein Family in the Gastrointestinal Tract

IGFBPs are a well-characterized family of six secreted proteins, designated IGFBP1–6, that bind IGFs with high affinity and display a broad spectrum of biological activity. Extensive information about the gene organization, protein structure, and molecular biology and physiology of IGFBPs can be found in the reviews referenced at the beginning of this section. The IGFBPs are potent modulators of IGF activity in the gastrointestinal tract, exerting both positive and negative effects, because their generally 10- to 100-fold greater affinity for IGFs than for the IGF receptors. Both IGF-I and IGF-II bind to all six IGFBPs, albeit with different affinity.

The structure of all six IGFBPs are similar due to their conserved evolution and can be divided into three domains: highly conserved C- and N-terminal domains, and a central domain that is unique among IGFBP family members. The C- and N-terminal domains bind IGFs. It is the central domain that is modified by posttranslational modifications and confers functional diversity among IGFBPs (7). Depending on the experimental setting and IGF function being assessed, IGFBPs may potentiate or inhibit IGF activity in the gastrointestinal tract primarily by altering the interaction of IGF-I or IGF-II with the IGF-IR. IGFBPs exert inhibitory effects by binding IGFs into a biologically inaccessible pool. Whereas stimulatory or potentiation of IGF action occurs by the facilitiation of IGFs binding with the IGF-IR. Regulated proteolysis of IGFBPs is a key mechanism for release of IGF and regulating its bioavailability to cells of the gastrointestinal tract (7). For example, addition of IGFBP-3 to colon cancer cell culture medium decreases bioactivity of IGF-I. Addition of MMP-7 cleaves IGFBP-3 into four fragments, releases IGF-I, and potentiates IGF-I biological activity (7). An important function of hepatic-derived IGFBP function is to transport IGFs made in the liver in the circulation and in extracellular fluids. IGFBPs are detectable in plasma and extracellular fluids and are expressed during GI tract development and into adult life. The primary hepatic derived IGFBP is IGFBP-3, which carries approximately 75% of circulating IGF-I and IGF-II bound to it and the co-carrier, ALS (7). Activities of IGFBPs (IGFBP-1, IGFBP-3, IGFBP-4 and IGFBP-5) in the gastrointestinal tract that are IGF-independent are also recognized. These play a role both in GI tract physiology and in pathophysiologic events. IGFBP-3 directly activates the TGF-βRI/II receptor complex and initiates Smad signaling in human intestinal smooth muscle cells (23, 24). In intestinal muscle cells, while IGFBP-5 facilitiates interaction of IGF-I with the IGF-

IR, it also acts independently of IGF-I to stimulate proliferation and further increase expression of IGF-I (Fig 2.) (25). Both processes involving IGFBP-3 and IGFBP-5 play a role in muscle hyperplasia in stricturing Crohn's disease but also the comcomitant excess collagen production.

IGFBP-3 and IGFBP-5 also possess COOH-terminal consensus nuclear localization sequences that allow cell entry and the direct nuclear activity of these binding proteins via a β-importin-dependent nuclear translocation mechanism. By this mechanism IGFBP-3 regulates apoptosis in prostate cancer cells, and IGFBP-5 regulates heterodimerization of RXR and vitamin D receptors and modulates vitamin-D-dependent differentiation (26, 27). A NH2-terminal sequence is a consensus transactivator domain that has been shown to possess strong IGF-I-independent transactivation activity (28). The participation of these mechanisms in gastrointestinal tract function has not yet been examined.

Biology of the Insulin-Like Growth Factor Family in the Gastrointestinal Tract

The gastrointestinal tract is a major target organ of IGF action (29). One of the most prominent effects is stimulation of intestinal epithelial cell and muscle cell proliferation and maintenance of cell survival by reduction of apoptosis. Other activities relate to the diverse effects of this ligand/receptor family on somatic growth, energy balance, and metabolism of glucose, carbohydrate, and proteins.

Insulin-Like Growth Factor Family Distribution in the Gastrointestinal Tract

The presence and distribution of IGFs and IGF receptors in the gastrointestinal tract has been extensively characterized (11,14,30–40). IGF-I, IGF-II, and IGFBPs are also present in human breast milk and in gastrointestinal tract secretions (41–43). A portion of enterally administered ^{125}I-IGF-I and ^{125}I-IGF-II can be recovered intact from gastrointestinal tissues of suckling rats, which indicates that the peptide is stable in the milieu of the neonatal stomach and small intestine (44, 45). While the expression of this ligand receptor system in the gastrointestinal epithelium is clear, a clear understanding of its distribution along the crypt-villus axis and in the epithelial-mesenchymal compartments has not emerged. It is clear that both IGF-I and IGF-II bind to intestinal epithelial cells (35,37,39,46, 47) and that IGF-IR and IGF-IIR are targeted to the basolateral membrane domain of the enterocyte (48,49). Multiple components of the IGF system, including IGFBPs, are expressed in subepithelial myofibroblasts and lamina propria in the gastrointestinal tract, implying an important role in regulation of epithelial-mesenchymal interactions (50,51). The intestinotrophic effects of IGF-I are mediated by GLP2-dependent regulation of myofibroblast IGF-I expression. In support of this, transgenic mice in which IGF-I is overexpressed in the intestinal lamina propria under the direction of an α-smooth muscle actin promoter show increased proliferation of the ileal epithelium (52).

Several other observations in transgenic mice are worth noting. In mice with an hepatic deletion of IGF-I, the gastrointestinal tract, including the muscularis propria, develops normally. However, while mice overexpressing IGF-I have a normal gastrointestinal epithelium but expanded submucosa, and the muscularis propria is hyperplastic and hypertrophic (53). C57BL/6J mice heterozygous for IGF-I [IGF-I(+/−)], have normal gastrointestinal development, but with a thinner submucosal compartment compared wildtype mice in the neonatal period (54). The hyperplasia and stricturing that occurs during the course of TNBS-induced colitis is markedly attenuated in IGF-I(+/−) mice (Fig 3) (55). In aggregate, these observations highlight the autocrine role of IGF-I produced in the gastrointestinal tract, particularly by smooth muscle cells of the gastrointestinal tract, in its growth, development and response to inflammation.

As noted earlier, most circulating IGF-I is synthesized in the liver under the regulation of GH. Consequently, hepatocyte levels of IGF-I are very high. IGFBPs are also synthesized in the liver. Interestingly, however, the normal hepatocyte is not considered a major target for IGF action, because of the extremely low level of IGF-IR expression (56). Hepatic stellate cells and myofibroblasts also express IGFBPs and IGF-I (57). It is these cells that are believed to play a pivotal role in the fibrogenic response to IGFs in the liver (58).

The expression of IGF-II and IGF-IIR are highly developmentally regulated. IGF-II RNA transcripts are readily detectable in the intestine during gestation, but are much less apparent in the adult rat (11,32). Similar observations have been made in human stomach and intestine (40). IGF-IIR levels similarly are developmentally regulated during rat and human intestinal development (11,59). IGFBP-2 has high affinity for IGF-II and tightly regulates IGF-II availability during fetal and early neonatal growhth (60). Overall these studies indicate that the IGF-II/IGF-IIR axis plays an important role in fetal intestinal development (40,59). A clear pattern of developmental expression of IGF-I/IGFIR has not emerged, however, IGF-I is generally recognized to be the predomant IGF-I in adult. Fluctuations in expression are observed and the degree of change is less apparent than that described for IGF-II (11,39,49,60).

Insulin-like Growth Factor Stimulates Cellular Proliferation

IGFs are mitogenic for intestinal epithelial and smooth muscle cells and for hepatic stellate cells *in vitro* and *in vivo*. *In vitro*, IGFs stimulate intestinal epithelial proliferation, but, in most instances, less so than other growth factors such as EGF (60,61,62–65). When EGF is provided with IGF-I or insulin, a synergistic effect on intestinal epithelial proliferation often is observed. Isolated intestinal smooth muscle cells and isolated hepatic stellate cells *in vitro* also proliferate in response to IGF-I (66,67).

In vivo evidence for a the proliferative effects of IGF on the intestinal epithelium are robust and derive from experimental models using both enteral and parenteral IGF-I. Oral feeding of IGF-I to neonatal pigs increases indices of small intestinal weight, DNA content, protein content, and villus height in the small intestine (68). *In utero* ligation of the esophagus in fetal sheep deprives the intestine from growth regulatory peptides in amniotic fluid. A 10-day infusion of IGF-I distal to the ligation results in increased small intestinal growth (69). A small increase in intestinal crypt labeling was seen even after a brief treatment of mice with intraperitoneal administration of IGF-I (70). A 14-day parenteral administration of IGF-I to adult rats increased crypt depth and villus height by 30% (71). In multiple models, infusion of LR^3IGF-I, an N-terminal–extended analogue of IGF-I that has a reduced affinity for IGFBPs, better stimulates proliferation in the epithelium and muscularis of the small intestine than the parent peptide (72,73). The effects of IGF-I in these studies are most prominent in the proximal intestine and are not seen not in the pancreas or stomach.

IGF-I also has important regulatory effects on intestinal growth in pathophysiologic conditions as well. Adaptive mucosal proliferation in the small intestine of rats that have undergone a partial small intestinal resection is increased by IGF-I (74–76). Atrophy of the jejunal mucosa in parenterally fed rats, is blunted by administration of inclusion of IGF-I in the parenteral nutrition (TPN) solution (77). Small intestinal atrophy occuring in the setting of chronic liver disease or sepsis is also reduced by administration of IGF-I (78,79). Fibrosis and stricture formation in patients with Crohn's disease and in animal models of ileocolitis, including TNBS-induced colitis, are associated with increased IGF-I expression and increased smooth muscle proliferation (21). Smooth muscle proliferation and fibrosis from TNBS-induced colitis are significantly diminshed in IGF-I(+/−) heterozygous mice (55).

Studies in transgenic mice also demonstrate the proliferative effect of GH or IGFs on the intestinal mucosa. Mice overexpressing GH have increased plasma and intestinal mucosal IGF-I levels, increased bowel length and mass, but normal intestinal crypt cell proliferation rate, indicative of GH-stimulated survival of intestinal epithelial cells (80). In mice overexpressing IGF-I under an MT-I promoter, circulating GH was undetectable, because of negative feedback from IGF-I, allowing determination of the specific effects of GH and IGF-I on the intestine. MT-IGF-I mice exhibit a significantly greater small intestinal length and mass, an increased villus height, greater crypt depth, and a higher crypt cell mitotic index compared with wildtype mice while differentiation was not altered (81). In contrast, transgenic overexpression of IGF-II has variable effects on mass of the gastrointestinal tract (82,83). Transgenic overexpression of IGFBP-3 was associated with increased liver mass (84). Trangenic overexpression of IGFBP-4 coupled to a smooth muscle α-actin promoter (SMP4/SMP8-IGFBP-4) induced hypoplasia of intestinal smooth muscle suggesting that IGFBP-4 acts as an endogenous inhibitor of IGF-I actions in intestinal smooth muscle. This was confirmed *in vitro* in human intestinal smooth muscle cells (85). A detailed analysis of the gastrointestinal effects of IGFBP deletion or overexpression has not been reported.

These studies suggest that IGF-I and GH, both of which are used extensively in the clinical arena for other indications, may be useful therapeutic agents in patients with short bowel syndrome and some studies suggest that GH improves intestinal function in patients with short bowel syndrome (86,87). In animal models and in humans studies of short bowel syndrome, intestinal atrophy, or inflammatory bowel disease, IGF-I is more potent in stimulating intestinal growth than GH. This may be because of induction of suppressor of cytokine signaling-2 (SOCS-2) by GH, but not IGF-I (88). More recently the role of GLP-2 in this respect has been examined. GLP-2 directly and indirectly, via induction of IGF-I expression, increases intestinal growth. In IGF-I null mice, the ability of GLP-2 to increase intestinal growth is lost (89). New clinical trials using IGF-I and in combination with GLP-2 may offer more encouraging results in subjects with decreased gastrointestinal mucosal function (90,91).

Insulin-like Growth Factor Is Pro-Survival

The studies discussed earlier indicate that IGFs increase intestinal growth, in part, by inhibition of apoptosis. MT-IGF-I transgenic mice have a lower basal level of apoptosis in small intestine crypts and a lower level of apoptosis in response to irradiation (92). This is consistent with studies showing that IGF-I inhibits apoptosis in cultured cells (93).

In vitro and *in vivo* studies demostrate that autocrine IGF-I in addition to stimulating proliferation inhibits apoptotis (promotes survival) in smooth muscle cells of the muscularis propria of humans and mice (55,94).

Insulin-like Growth Factor Is Profibrogenic

Several lines of investigation demostrate the profibrogenic actions of IGFs in the intestinal tract. IGF-I not only stimulates proliferation and inhibits apoptosis of fibroblasts, myofibroblasts, and smooth muscle cells, it also increases collagen expression and production in each of these cells (95,96). In SMP8-IGF-I mice, transgenic expression of IGF-I increases the mass of the muscularis propria and length of the intestine (53,55). The adaptive response to surgical resection of the small intestine in this same SMP8-IGF-I mouse is characterized by a marked lengthening of the residual bowel, suggesting IGF-I autocrine activity increases the mesenchymal elements in the intestine (97). In Crohn's disease, a human disorder characterized by fibrosis and stricture formation, mucosal IGF-I and IGF-IR levels are increased relative to normal intestine as are muscularis propria IGF-I, IGFBP-3 and IGFBP-5 levels. In human intestinal muscle the predominant collagen isotype

is collagen IαI. In these cells and in animal models of Crohn's disease (eg TNBS-induced colitis), the increased IGF-I, IGFBP-3 and IGFBP-5 levels (and increased TGF-β1 levels) that are present in the inflamed intestine, individually and in concert, stimulate collagen IαI expression leading to increased collagen secretion and fibrosis (Fig 4.) (24,25, 55,98). It is noteworthy that a profibrogenic response to IGF-I in all regions of the gastrointestinal tract is not seen. In the liver, carbon tetrachloride injury in the SMP8-IGF-I mouse, results in reduced collagen synthesis and amelioration of the extent of liver injury (99).

Insulin-like Growth Factor in Gastrointestinal Cancers

The prominent effects of IGF ligands mediated via IGF receptors on cellular proliferation and survival suggest that the IGF axis may play an important role in the development of dysplasia and neoplasia. Multiple lines of investigation have supported this view (6,8). While circulating IGF-I levels vary considerably among healthy individuals, population-based studies suggest an overall trend toward increasing cancer risk, including cancers of the gastrointestinal tract, in persons at the high end of the normal range of IGF-I blood levels. Loss of IGF-II imprinting results in a modest increase in IGF-II levels, and is now widely accepted as a marker for colorectal cancer risk (15). Increased expression of IGF-I, IGF-II, and IGF-IR are observed in colorectal cancers (100). IGF-II overexpressing mice treated with 1,2-dimethylhydrazine to induce neoplastic alteration promoted the growth of colonic aberrant crypt foci and increased colonic tumor volume without affecting tumor numbers compared to wildtype mice (101). Transgenic overexpression of IGFBP-2, which has high affinity for IGF-II, reduced the appearance of dysplastic aberant crypt foci and inhibited tumor growth in the same model (102).

IGFBP-3 has been shown to promote TGF-β1-mediated epithelial to mesenchymal transition (EMT) and tumor cell invasion in esophageal cancer (103). Interestingly, these effects appeared to be mediated independent of IGF-I.

SUMMARY

The liver is a major source of IGF's and IGFBP's that are present in the circulation and have important endocrine activities relating to energy metabolism, body size, carcinogenesis, and various organ specific functions. While IGFs have only minor effects on the normal liver itself, production of IGF's and IGFBP's in a tissue specific fashion in the gastrointestinal tract exert important regulatory effects, via autocine and paracrine mechanisms, on cellular proliferation, survival, and apoptosis. IGF's and IGFBP's play important regulatory roles in the response of both the liver and the gastrointestinal tract to inflammation and in the development of neoplasia.

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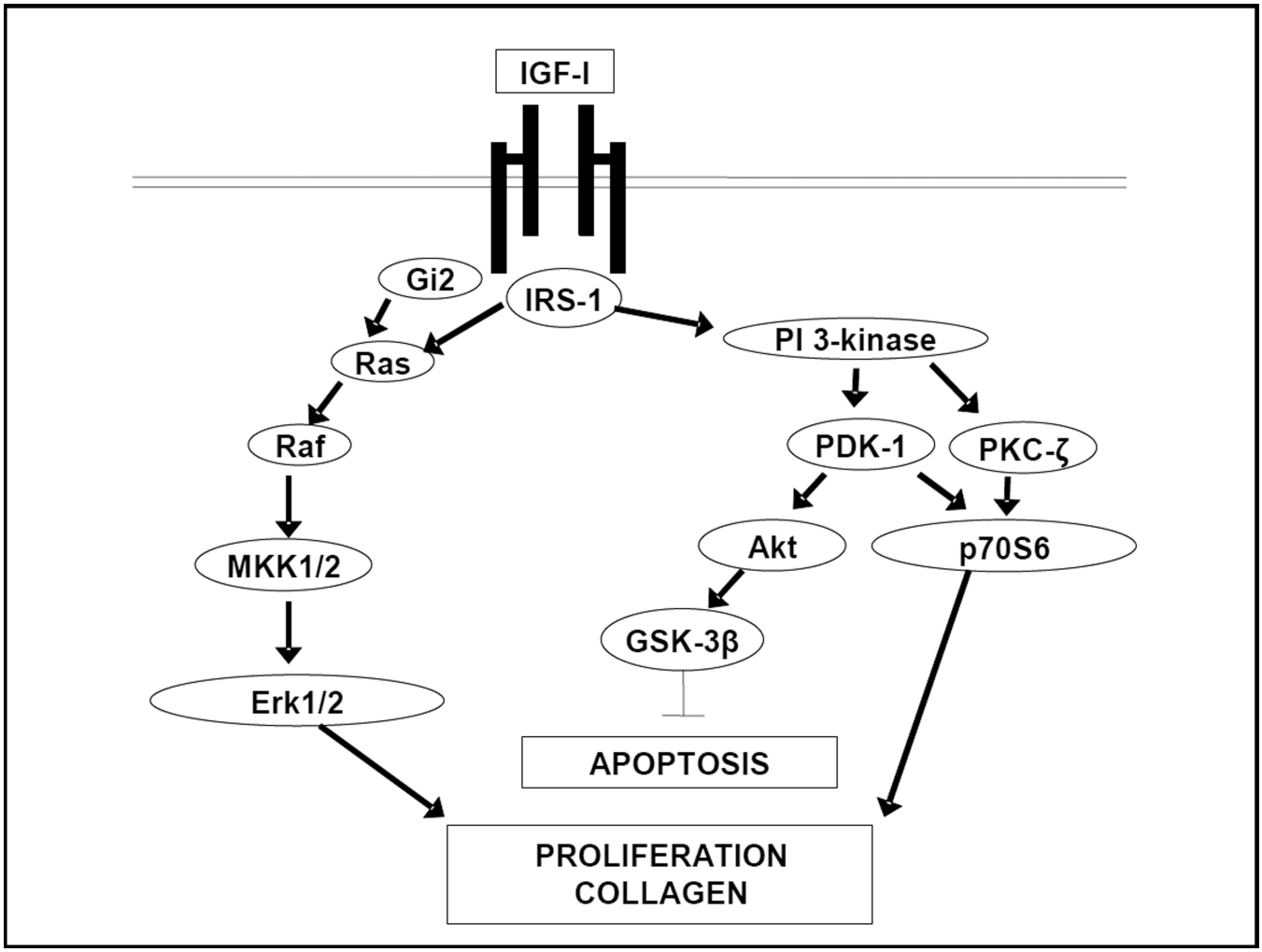

Figure 1.

Signaling cascades activated by the activated IGF-I receptor. The IGF-I receptor is located on the basolateral membrane of intestinal epithelial cells and on smooth muscle cells. Ligand binding and activation of the IGF-I receptor elicts phosphrylation of cytoplasmic tyrosine residues in this receptor tyrosine kinase. Subsequently binding of scaffolding and docking proteins results in activation of distinct intracellular signaling cascades that regulate proliferation and survival and collagen IαI expression.

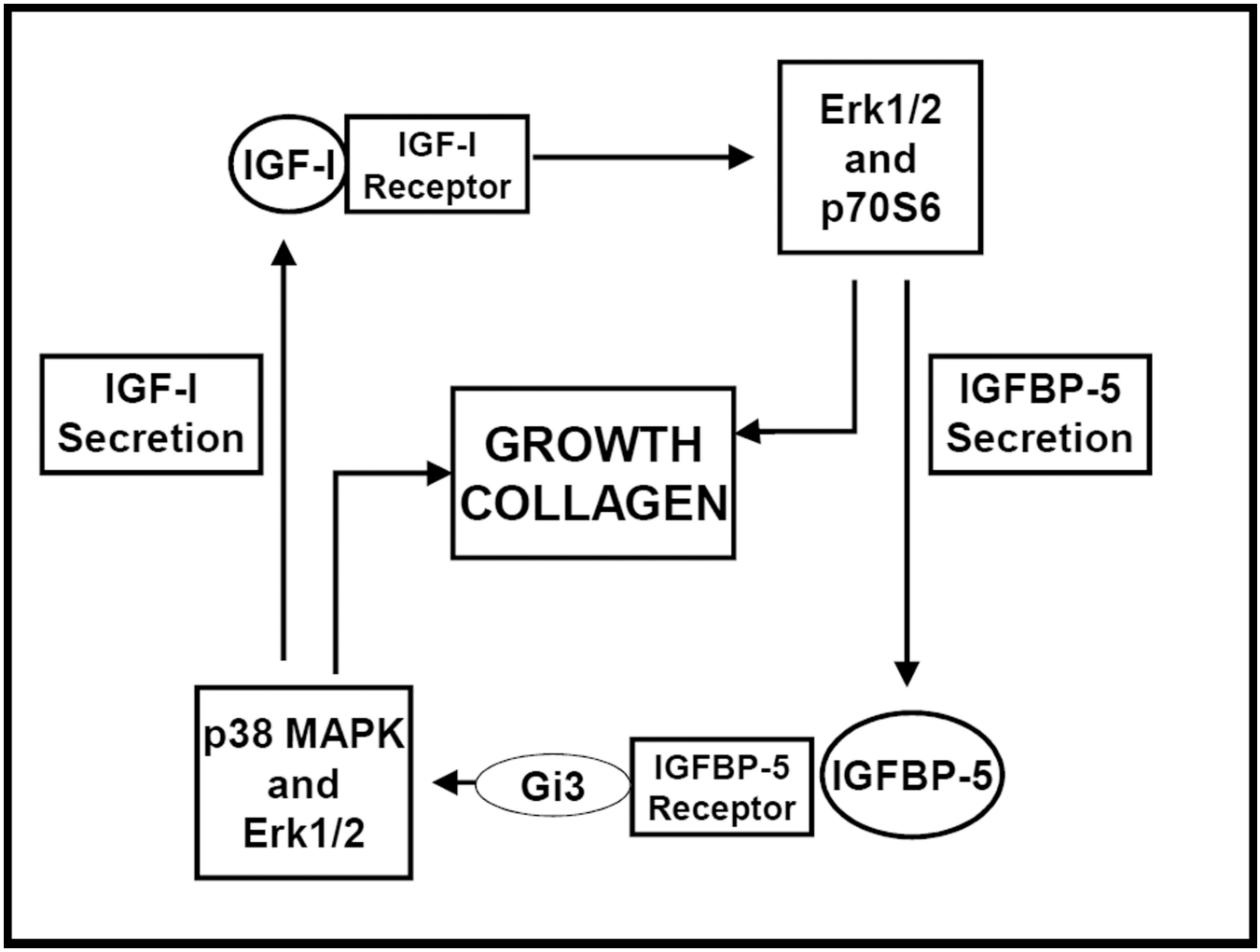

Figure 2.
Positive feedback between IGFBP-5 and IGF-I. The expression and effects of IGF-I and IGFBP-5 are linked whereby IGF-I stimulates IGFBP-5 expression and IGFBP-5, independent of IGF-I, stimulates IGF-I expression each reinforcing the expression and effects of the other.

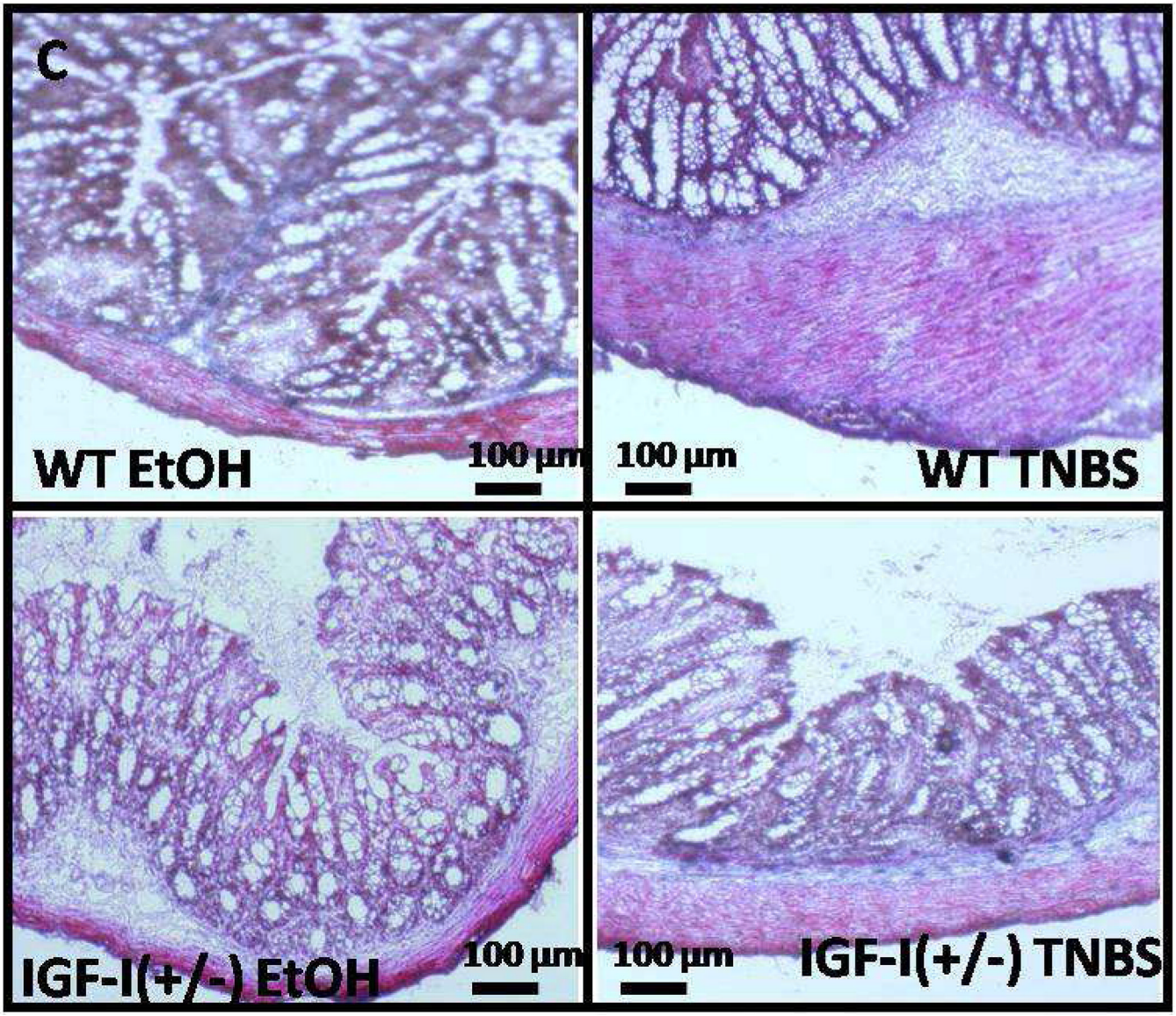

Figure 3.
Inflammation-induced fibrosis is decreased in IGF-I(+/−) mice. Collagen deposition in smooth muscle layer of vehicle-treated IGF-I(+/−) mice and its increase in response to TNBS-induced colitis are lower than in wildtype C57BL/6J mice.

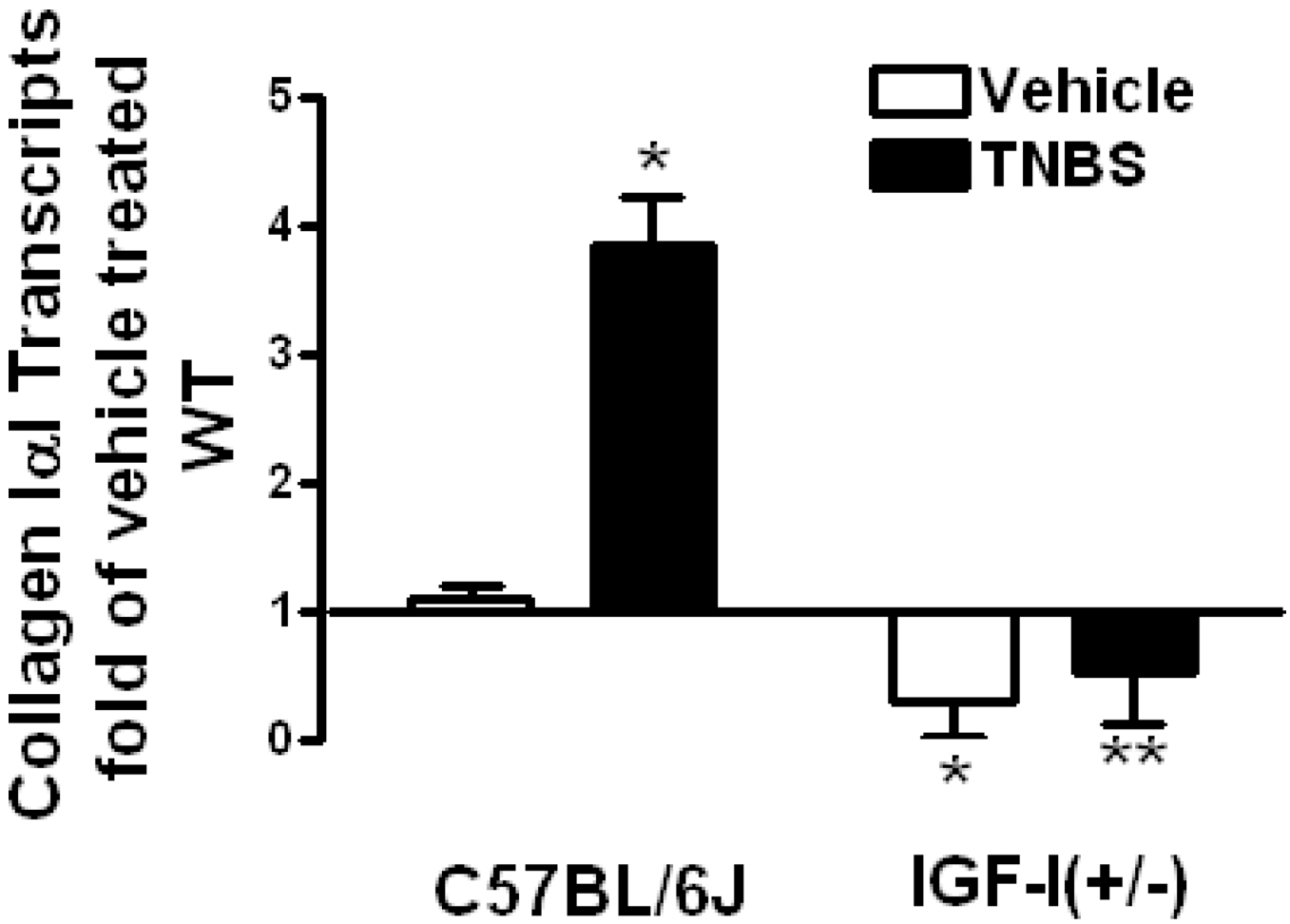

Figure 4.

Inflammation-induced collagen IαI expression is decreased in IGF-I(+/−) mice. Collagen IαI transcripts in smooth muscle cells of vehicle-treated IGF-I(+/−) mice and its increase in response to TNBS-induced colitis are lower than in wildtype C57BL/6J mice. Transcript levels were measured by real-time PCR using the $2^{-\Delta\Delta Ct}$ method.