REVIEW

Insulin, Insulin-Like Growth Factor-I (IGF-I), IGF Binding Proteins, Their Biologic Interactions, and Colorectal Cancer

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Secular changes and worldwide variations in incidence rates of colorectal cancer, along with results from twin and migrant studies, provide compelling evidence that environmental factors influence the risk of this disease. Among the most important of these factors are diet and associated factors, such as physical activity and body size. Recent data suggest that dietary and related factors may influence colorectal cancer risk via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I). Epidemiologic studies have shown that IGF-I is positively associated with the risk of colorectal cancer, and experimental studies have shown that IGF-I has mitogenic and antiapoptotic actions on colorectal cancer cells. IGF-I bioactivity is regulated in part by its six binding proteins (IGFBP-1 to IGFBP-6); insulin inhibits the production of IGFBP-1 and perhaps IGFBP-2. As a result, chronically elevated fasting and postprandial insulin levels may lead to a decrease in circulating IGFBP-1 and IGFBP-2 concentrations and, consequently, an increase in IGF-I bioavailability. Insulin may also increase the circulating IGF-I/IGFBP-3 ratio by increasing hepatic growth hormone sensitivity. The increased IGF-I bioavailability may, over time, increase the risk of colorectal cancer. This new evidence for biologic interactions among insulin, IGF-I, and IGFBPs in the context of colorectal carcinogenesis provides a potential mechanism through which diet and associated factors may increase the risk of this cancer. [J Natl Cancer Inst 2002;94:972–80]

Colorectal cancer is a major cause of morbidity and mortality throughout the world. In 1996, an estimated 875 000 new cases were diagnosed worldwide *(1).* High-risk areas include North America, Europe, and Australia, which account for nearly two thirds of the total global incidence; however, incidence is now rapidly increasing in areas that were previously at low risk, such as Latin America, Asia, and Africa. These secular changes and the worldwide variations in incidence rates, taken together with the results of twin and migrant studies, provide compelling evidence that environmental factors influence the risk of colorectal cancer *(2,3).* Indeed, only 5%–10% of all colorectal cancer cases are the result of known genetic syndromes *(2).* However, the impact of gene–environment interactions in colorectal cancer etiology is uncertain. Of the environmental risk factors, diet and associated factors, such as physical activity and body size, are thought to be among the most important. Obesity (particularly of the upper body), physical inactivity, and diets that are low in vegetables, fruits, and fiber and high in meat, saturated fats, refined carbohydrates, and processed foods have all been associated with an increased risk of colorectal cancer *(2,4).* Recent data suggest that the increased risk of colorectal carcinoma may result from the possible influences of dietary and related factors on blood insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I) *(4,5).*

In this review, we integrate and assess data from the scientific literature relating to insulin and its biologic interactions with IGF-I and insulin-like growth factor binding proteins (IGFBPs) in the context of colorectal carcinoma. To this end, we critically assess data from experimental, clinical, and observational studies that have investigated the physiologic and pathophysiologic role of IGF-I and its binding proteins and how they relate to insulin levels. A model for colorectal carcinogenesis based on these biologic interactions will also be described. We end by outlining possible therapeutic and preventive strategies and providing suggestions for future research.

Insulin and Colorectal Cancer

Increased blood insulin concentration (hyperinsulinemia), which can be caused by both genetic and environmental factors, is characterized by raised fasting plasma insulin levels and an exaggerated insulin response to increases in plasma glucose concentrations. Hyperinsulinemia is a compensatory response that maintains glucose homeostasis in individuals who become resistant to insulin action *(6).* With increasing insulin resistance, pancreatic β-cells synthesize and secrete increasing amounts of insulin. However, hyperglycemia prevails when pancreatic β-cells can no longer compensate for increasing insulin requirements, ultimately resulting in the development of type 2 diabetes mellitus. In individuals with advanced hyperglycemia and type 2 diabetes, pancreatic β-cell function may eventually become impaired, leading to reduced insulin production and hypoinsulinemia.

Recent prospective observational studies *(7–9)* have shown that colorectal adenomas and cancer are positively, albeit moderately, associated with type 2 diabetes. Such associations are consistent with reports that hyperglycemia is associated with an increased risk of colorectal cancer *(10–12).* These results, to-

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See "Notes" following "References."

gether with the marked and consistent similarities in the dietary and lifestyle risk factors for type 2 diabetes and colorectal cancer *(4),* have led to the suggestion that hyperinsulinemia might underlie the link between type 2 diabetes and colorectal cancer *(4,7,8).* Indeed, both cross-sectional and prospective population studies *(10–12)* have found that colorectal cancer is more common in people with hyperinsulinemia and its metabolic correlates, including hypertriglyceridemia. Of the two prospective studies, one *(11)* found a statistically significant twofold higher risk of colorectal cancer among people in the highest quartile of serum insulin concentrations compared with those in the lowest after more than 6 years of follow-up. The other study *(5)* found a statistically significant, nearly threefold increased risk of colorectal cancer in individuals in the highest quintile of serum C-peptide (a marker of pancreatic insulin secretion) compared with individuals in the lowest quintile.

These epidemiologic observations are consistent with *in vivo* experimental studies *(13–16)* that demonstrate growth-promoting effects of exogenous insulin, dietary-induced hyperinsulinemia, and hypertriglyceridemia on colon cancer and aberrant crypt foci, a putative precursor of colon cancer. In addition, insulin has been shown to increase the growth of colon epithelial and carcinoma cells *in vitro (17,18).*

Taken together, these results indicate that insulin may play an important role in colorectal carcinogenesis. It has been suggested that insulin may promote colorectal carcinogenesis directly by activating its own receptor, the receptors for IGF-I, or hybrid insulin/IGF-I receptors *(4),* all of which are expressed by colorectal epithelial and carcinoma cells *(19).* However, such direct action is unlikely because insulin has been found to be a relatively weak mitogen *in vitro,* acting as such only at very high concentrations *(4,18).* In addition, insulin has extremely low affinity for IGF-I receptors and competes poorly with IGF-I for binding to hybrid insulin/IGF-I receptors *(20).* An alternative model proposes that insulin acts indirectly to promote colorectal carcinogenesis. In this model, consumption of excess dietary energy results in the development of insulin resistance, which is characterized by increased circulating levels of insulin, triglycerides, and nonesterified fatty acids. These circulating factors may, in turn, initiate a general proliferative response from colonic epithelial cells and promote colorectal carcinogenesis *(21).*

A third model for the role of insulin in colorectal carcinogenesis is supported by recent experimental and observational studies that implicate IGF-I, a potent mediator of cell survival and growth, in the etiology of colorectal cancer *(19,22,23).* Specifically, elevated circulating levels of insulin may lead to increased IGF-I bioavailability as a result of insulin-mediated changes in IGFBP concentrations *(5,24).* Thus, chronic hyperinsulinemia may indirectly promote colorectal carcinogenesis by inducing pathophysiologic changes in concentrations of circulating IGF-I and IGFBPs *(5).*

IGF-I Physiology

The IGF family of peptide ligands (IGF-I and IGF-II), the IGF-I and IGF-II receptors, the six IGFBPs, and the IGFBP proteases are fundamentally involved in the regulation of somatic growth, cell proliferation, transformation, and apoptosis *(20,25–30).* IGF-I may also have important effects on metabolism. Indeed, *in vivo* infusions of recombinant human IGF-I are associated with acute decreases in circulating glucose concentrations, which are thought to be due to IGF-I-mediated increases in insulin sensitivity and glucose uptake by skeletal muscle, either directly, through its receptor, or indirectly, via its inhibitory effect on growth hormone (GH) secretion *(24).*

IGF-I stimulates growth and metabolism by binding to the IGF-I receptor, thereby activating a protein tyrosine phosphorylation signal transduction cascade that is similar to the one involved in insulin action *(31).* The liver is the major source of IGF-I *(32),* with both hepatic and peripheral production being mainly regulated by GH *(20).* Higher GH levels lead to increased concentrations of circulating IGF-I. Other hormonal, genetic, and nutritional factors may also be important determinants of intra- and inter-individual variability in IGF-I *(20,33–35).*

Most circulating IGF-I is bound to the IGFBPs, especially IGFBP-3, which binds more than 90% of the circulating IGF-I in a 150-kd ternary complex consisting of IGF-I, IGFBP-3, and an 80-kd acid-labile subunit. In this form, IGFBP-3 sequesters IGF-I in the vascular system, increasing its half-life and providing an IGF-I reservoir. Other IGFBPs form binary complexes with IGF-I that may cross the capillary boundary, allowing selective transport of IGF-I to various tissues. IGFBPs generally inhibit IGF-I action by binding competitively to it and thereby reducing its bioavailability; however, in some cases, they appear to enhance IGF-I activity or to act independently of IGF-I *(20,36).* Cleavage of IGFBPs by their specific proteases also influences IGF-I bioavailability by reducing the amount of bioavailable IGFBPs. Overall IGF-I bioactivity *in vivo,* therefore, represents the combined effect of interactions involving endocrine, autocrine, and paracrine sources of IGF-I, IGFBPs, and IGFBP proteases.

The IGFBPs are produced by a variety of different tissues via complex regulatory processes. Similar to IGF-I, GH stimulates the production of hepatic IGFBP-3 and its acid-labile subunit, which is the major source of circulating IGFBP-3 and its acid-labile subunit *(36).* However, whereas insulin is the primary regulator of hepatic IGFBP-1 production, relatively little is known about the principal regulatory mechanisms that control expression of IGFBP-2, IGFBP-4, IGFBP-5, and IGFBP-6 *(26,33,36).*

IGF-I and Colorectal Cancer

Clinical Studies

Recently, accumulating evidence has suggested that GH and IGF-I may be important components of the pathophysiologic mechanisms that underlie the growth of neoplasms, including colorectal carcinoma *(27–30).* For example, patients with acromegaly, who have elevated levels of circulating GH and IGF-I, may be at increased risk of developing colorectal adenoma and carcinoma *(37,38),* although reports are inconsistent and may be prone to bias. Moreover, colorectal mucosal cell proliferation rates in the sigmoid colon of acromegalics correlate with serum IGF-I concentrations and are substantially higher in acromegalics than in nonacromegalics *(39).* In addition, acromegalics with newly detected adenomas at follow-up colonoscopy have higher serum IGF-I concentrations than acromegalic patients without new adenomas *(40).*

Prospective Observational Studies

A number of prospective studies have also found that physiologic variations in GH and IGF-I are associated with changes in

cancer incidence and mortality. For example, healthy men with high serum GH levels have a statistically significantly increased risk of mortality from cancer compared with healthy men with low serum GH levels *(41).* In addition, two recent prospective epidemiologic studies *(22,23)* have shown that higher plasma IGF-I and lower plasma IGFBP-3 concentrations are associated with an increased risk of colorectal adenoma and cancer among both men and women. However, the associations between IGF-I and IGFBP-3 and risk of colorectal cancer were statistically significant only after adjustment for each other *(22,23).* One of the studies *(23)* found a fourfold increased risk of colorectal cancer in men who were in both the highest tertile of IGF-I and lowest tertile of IGFBP-3 compared with that of men in the lowest tertiles of both IGF-I and IGFBP-3. Both studies noted that high levels of IGFBP-3, independently of IGF-I, were associated with a lower risk of colorectal adenoma and cancer.

These observations suggest that the ratio of circulating IGF-I/IGFBP-3 may be a marker of circulating and tissue IGF-I bioavailability. As noted earlier, GH increases hepatic production of both IGF-I and IGFBP-3, which, at least in part, may account for the positive association between circulating levels of IGF-I and IGFBP-3. Studies of acromegalics and nonacromegalic control subjects *(42,43)* have also shown that the IGF-I/IGFBP-3 ratio increases with increasing serum GH concentrations, indicating that GH differentially stimulates IGF-I and IGFBP-3 secretion. Experimental data suggest that IGF-I itself may also regulate hepatic IGFBP-3 production *(44).*

However, a subsequent prospective study *(5)* found different results than the earlier studies: Women in the highest quintile of serum IGFBP-3 had a statistically significantly increased risk of colorectal cancer compared with women in the lowest quintile. Furthermore, this effect was not independent of serum IGF-I levels. In a more recent prospective study of Chinese men living in Shanghai *(45),* a secondary analysis of case patients diagnosed within 8 years of follow-up also found that IGFBP-3 was positively associated with risk of colorectal cancer. In this study, high serum levels of IGF-II, but not IGF-I, were associated with an increased risk of colorectal cancer. It is possible that the different findings may be the result of variations in the specificity of laboratory assay techniques for intact and proteolytically cleaved IGFBP-3 *(46).*

It is also possible that some physiologic mechanism underlies these divergent findings. The inconsistent results for the association of IGFBP-3 with colorectal cancer risk imply that there may be other important determinants of IGFBP-3 and IGF-I bioavailability and bioactivity, possibly including IGFBP-3-specific proteases and their regulators *(36).* Clinical studies have revealed that co-administration of IGF-I and IGFBP-3 does not inhibit the hypoglycemic action of IGF-I, and *in vivo* studies have shown that IGFBP-3 infusion or overexpression does not attenuate glucose tolerance *(47,48).* The dual role of the IGFBPs as both inhibitors and enhancers of IGF-I bioactivity may also explain the inconsistent associations between IGFBP-3 and risk of colorectal cancer *(20,36).* For example, differences in the relative affinity of IGF-I for its receptor and for IGFBPs have been proposed to contribute to IGFBP-3 enhancement of IGF-I function *(36).*

Experimental Studies

Additional evidence for the role of IGF-I and its binding proteins in colorectal carcinogenesis comes from *in vitro* models, which have shown that IGFs have potent antiapoptotic and mitogenic properties in both normal and neoplastic cells *(27–29).* These data suggest that IGF-I may play a role in various stages of cancer progression. Colorectal epithelia and cancer cells express IGF-I receptors, which stimulate mitogenesis when activated by IGF-I *in vitro (17,18,49,50).* Moreover, IGF-I receptor mRNA expression is increased in human colorectal carcinoma cell lines *(50,51);* conversely, blockade of the IGF-I receptor inhibits survival and growth of human colorectal cancer cells *(52,53).* The phosphorylated tyrosine residues of an activated IGF-I receptor serve as docking sites for a variety of intracellular signaling molecules, including Shc, PI3 kinase, Grb2, Grb10, PLCγ1, IRS-1, and IRS-2 *(54).* Depending on the cell type, IGF-I receptor activation and recruitment of these downstream effectors induces proliferation, differentiation, or inhibition of apoptosis. These signaling pathways may also be differentially regulated by the relative availability of immediate intracellular receptor substrates *(55,56).*

The IGF-I signal transduction pathway involved in the regulation of apoptosis and mitogenicity is also partly mediated by activation of the Ras protein *(20,57).* Farnesylation of Ras, catalyzed by farnesyl transferase, is required for its functional and transforming capabilities. Insulin promotes Ras farnesylation and may therefore prime cellular responses to IGF-I *(58).* Mutant Ras proteins with increased activity are found in approximately half of all colonic tumors and may promote the growth of adenomas into carcinomas.

IGF-I can also induce the expression of vascular endothelial growth factor, thus promoting colorectal tumor progression by inducing the development of blood vessels *(59).* This growth-promoting role of IGF-I is in contrast to the IGF-I-independent growth inhibitory effect of IGFBP-3, which has been shown to enhance p53-dependent apoptosis and differentiation in colonic epithelial cells *(60).*

Circulating and Tissue IGF-I Levels

Although it is well documented that IGF-I can promote carcinogenesis at the cellular level, it is unclear whether circulating IGF-I can do so as well. Accumulating evidence indicates that this may be the case. For example, as already mentioned, investigations of acromegalics suggest that rates of colorectal mucosal cell proliferation are associated with circulating IGF-I levels *(39).* Similarly, reduction of serum IGF-I by dietary restriction in animal models slows tumor progression and increases apoptosis in tumor cells—effects that are both reversed by infusions of recombinant IGF-I *(61,62).* Likewise, infusions of recombinant GH and IGF-I have been found to promote tumor growth *in vivo (63).*

More recently, hepatic IGF-I gene deletion mice have been created that show a 75% reduction in circulating IGF-I levels *(32,44).* Orthotopic transplantation of adenocarcinoma cells into the cecum of control and transgenic mice has shown that the incidence of tumor growth and hepatic metastasis was statistically significantly higher in control animals *(64).* Moreover, in both control and transgenic mice, treatment with recombinant human IGF-I led to statistically significantly increased rates of tumor development and metastatis to the liver. Although transgenic mice have dramatically reduced circulating IGF-I levels, they also exhibit compensatory GH hypersecretion *(44),* which suggests that the decreased rates of tumor development and me-

tastases seen in these animals may be directly attributable to the lower circulating IGF-I levels.

Investigators have also noted that absence of the wild-type allele of a microsatellite polymorphism in the promoter region of the IGF-I gene is associated with low circulating IGF-I concentrations and an increased risk of type 2 diabetes and myocardial infarction *(65).* This IGF-I genetic polymorphism may represent the effects of long-term exposure to IGF-I at both the tissue and circulatory levels. Similarly, a recently identified single nucleotide (T to A) polymorphism in the human growth hormone gene, GH1, has been associated with a reduced risk of colorectal cancer *(66).* Specifically, this study found that A/A individuals had a statistically significantly reduced risk of colorectal cancer and relatively lower circulating concentrations of IGF-I and the IGF-I/IGFBP-3 ratio than T/T individuals. The study also showed a similar association for colorectal adenomas.

The above gene association study *(66)* was conducted in an ethnically diverse population consisting of Japanese, Native Hawaiians, and Caucasians. However, the association between the GH1 genetic polymorphism and risk of colorectal cancer was not evident in the Japanese study subjects, even though the GH1 polymorphism was related to circulating IGF-I concentrations in this ethnic group. This finding is consistent with an earlier prospective study of Chinese men *(45),* which found no association between circulating IGF-I concentrations and risk of colorectal cancer. Thus, environmental and lifestyle differences, as well as other unidentified genetic factors, may explain differences in risk among ethnic groups seen in prospective observational studies assessing the association between circulating IGF-I concentrations and subsequent risk of colorectal cancer.

Biologic Interactions Among Insulin, IGF-I, and IGFBPs

Experimental and Clinical Studies

The processes that link nutrition and growth are thought to involve complex interactions among insulin, GH, IGF-I, and IGFBPs (Fig. 1). Short-term changes in nutritional status do not substantially alter serum concentrations of IGF-I and IGFBP-3; however, during prolonged fasting and severe nutrient restriction, circulating levels of IGF-I and, to a lesser extent, IGFBP-3 decrease, whereas circulating levels of IGFBP-1 and IGFBP-2 increase *(24,33,67).* The opposite is observed during refeeding *(67,68).*

The decrease in circulating IGF-I and IGFBP-3 during long-term fasting occurs despite elevated levels of GH, the primary regulator of hepatic production of IGF-I and IGFBP-3 *(33,69).* Administration of GH during fasting also does not substantially increase IGF-I concentrations *(70),* probably because of the development of a GH-resistant state *(67).* This condition is the result of decreased hepatic GH receptor number and function, both of which are partially regulated by insulin *(20,33,67).*

Rapid changes in serum IGFBP-1 concentrations are regulated primarily by changes in insulin levels, and several studies *(69,71,72)* have shown that insulin inhibits the synthesis of IGFBP-1 in the liver. Low-insulin states, including long- and short-term fasting or poorly controlled type 1 diabetes, are characterized by elevated serum IGFBP-1 levels *(67,69,73,74).* Conversely, individuals with chronic hyperinsulinemia or whose serum insulin concentration is temporarily raised, such as during the postprandial period, during insulin infusions in healthy control individuals, and among people with obesity, insulinomas, or congenital hyperinsulinism with hypoglycemia, all show statistically significantly lower serum IGFBP-1 levels than control subjects *(68,71,75,76).*

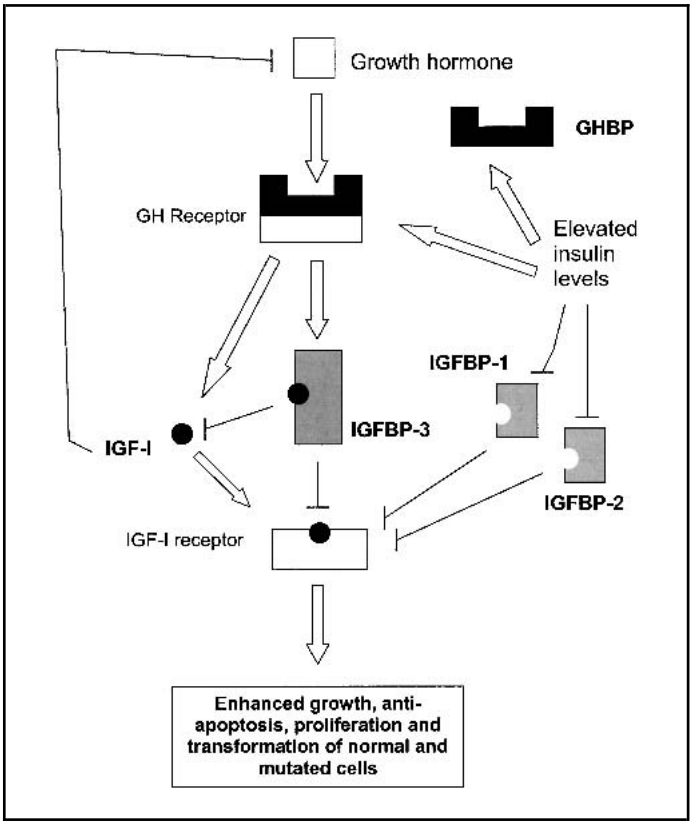

Fig. 1. Biologic interactions at the pituitary and hepatic levels among insulin, growth hormone (GH), insulin-like growth factor-I (IGF-I), and insulin-like growth factor binding proteins (IGFBPs). **Open arrows** denote stimulation, and **thin black lines** denote inhibition. Elevated insulin levels (**at right**) may indirectly increase the bioavailability of IGF-I (**solid circles**) by suppressing the production of IGFBP-1 and, to a lesser extent, IGFBP-2 (**shaded symbols**). In turn, increased IGF-I bioavailability may increase negative feedback effect on GH (**open square**), leading to reduced GH secretion and lower hepatic production of IGF-I and IGFBP-3. However, elevated insulin levels may also increase hepatic GH receptor (**open bar**) number and activity, reflected by increases in levels of circulating growth hormone binding protein (GHBP). This effect may lead to a rise in GH-regulated hepatic IGF-I and IGFBP-3 production, with a greater increase in levels of circulating IGF-I relative to IGFBP-3. Thus, along with genetic, hormonal, and other environmental factors, the relative magnitude of these two opposing effects of insulin on IGF-I production could determine levels of circulating IGF-I. Over time, excessive IGF-I bioavailability might increase the risk of colorectal cancer by promoting the survival of transformed and mutated cells that would normally undergo apoptosis.

Levels of IGFBP-2, unlike IGFBP-1, do not respond directly to acute changes in insulin or nutritional status *(33).* However, circulating levels of IGFBP-2 are elevated with prolonged fasting *(77),* and the elevation is more pronounced during protein restriction than during caloric restriction *(67).* Individuals with low insulin levels (e.g., patients suffering from malnutrition, anorexia nervosa, or untreated type 1 diabetes) also have elevated levels of IGFBP-2 *(78–80).* Moreover, in previously untreated type 1 diabetics treated with insulin, IGFBP-2 levels return to normal *(80).* These conditions of high IGFBP-2 concentrations are in contrast to the low levels of IGFBP-2 found in the chronically obese, which may be the result of obesity-related chronic hyperinsulinemia or its correlates, including changes in

circulating lipid concentrations *(36,81).* Therefore, long-term changes in circulating insulin concentrations may also result in substantial changes in circulating levels of IGFBP-2.

Collectively, these data indicate that insulin and its metabolic correlates may regulate levels of both IGFBP-1 and IGFBP-2 and, as a result, levels of bioavailable IGF-I. Both *in vitro* and *in vivo* studies *(36,71)* have shown that IGFBP-1 inhibits IGF-I-stimulated growth and differentiation and counteracts the potent insulin-like hypoglycemic activity of IGF-I *(82,83).* These observations imply that insulin-mediated changes in IGFBP-1 concentrations determine the amount of putatively free bioactive IGF-1 in circulation, a conclusion that is supported by the consistently observed inverse association between IGFBP-1 and free or readily dissociable IGF-I *(24,33,71,72).* A randomized trial *(83)* investigating the effects of continuous subcutaneous administration of IGF-I in humans found a further twofold increase in free IGF-I with a concomitant decrease in serum IGFBP-1 during a hyperinsulinemic clamp, in which insulin is infused at a constant rate to achieve physiologic suprabasal levels. This finding is compatible with the finding that obesity-related hyperinsulinemia is associated with statistically significantly higher levels of free IGF-I and lower levels of IGFBP-1 and IGFBP-2 than those found in nonobese adults and children *(81,84).*

The insulin-mediated increase in bioavailable IGF-I may also explain the paradoxical situation in which individuals with obesity or type 1 diabetes, despite having normal concentrations of total IGF-I, are characterized by hyposomatropinemia and hypersomatropinemia, respectively *(85).* In obese individuals, elevated free IGF-I may, as a result of hyperinsulinemia-induced IGFBP-1 suppression, increase IGF-I feedback to the pituitary gland to inhibit GH production. Consistent with this hypothesis is the finding that recovery of GH production following withdrawal of exogenous IGF-I administration is associated with changes in free rather than total IGF-I *(86).* Because IGF-I levels are normal in obese individuals, the low GH concentration indicates that insulin may increase GH-stimulated hepatic IGF-I synthesis via increases in hepatic GH receptor sensitivity or expression, as noted earlier *(67,81,85).* The increase in GH receptor levels is thought to be mirrored by plasma GH binding protein (GHBP) concentrations, which are elevated in obese individuals *(85).*

In addition, because GH differentially stimulates IGF-I and IGFBP-3 production, with a greater increase in IGF-I production, insulin may also indirectly increase total IGF-I levels *(67,73,81,83,85).* Studies of patients with type 1 diabetes have shown that insulin levels are positively correlated with serum IGF-I concentrations and that insulin withdrawal in such patients is associated with a substantial decrease in total IGF-I that can be reversed following insulin infusion *(73,83,87).* These insulin-associated increases in serum total IGF-I occur despite relatively small or no changes in serum IGFBP-3 and GH *(71).* Thus, insulin may also indirectly increase the circulating IGF-I/IGFBP-3 ratio *(83).* However, the relative magnitude of the two opposing effects of insulin on circulating IGF-I concentrations—i.e., increasing hepatic GH sensitivity via receptor up-regulation (which increases IGF-I levels) and increasing IGF-I negative feedback on GH production via suppression of specific IGFBPs and increased IGF-I bioavailability (which decreases IGF-I levels)—is likely be the main determinant of circulating IGF-I.

Collectively, these studies suggest that hyperinsulinemia-induced changes in the levels of IGF-I and IGFBPs may increase IGF-I bioavailability (Fig. 1). Specifically, chronically elevated fasting and postprandial insulin levels may lead to a decrease in circulating IGFBP-1 and IGFBP-2 levels and to a possible increase in the circulating IGF-I/IGFBP-3 ratio.

Role in Colorectal Cancer

The long-term increase in IGF-I bioavailability may, over time, increase the risk of colorectal cancer. Indeed, Kaaks et al. *(5),* in a prospective observational study, showed that increased serum IGFBP-1 and IGFBP-2 are inversely associated with colorectal cancer risk and that serum C-peptide and IGF-I are positively associated with colorectal cancer risk. This finding, along with data relating to the biologic interactions among insulin, IGF-I, and IGFBPs, provides a potential mechanism through which previously identified environmental factors, such as diet and associated lifestyle factors, including high saturated fat and meat consumption, low physical activity, and obesity, may operate to increase the risk of this cancer *(2,4,10).*

Colorectal carcinogenesis is a multifactorial and multistep process that involves an accumulation of genetic mutations *(88).* These mutations occur spontaneously throughout life; the rate at which they occur may be increased by both exogenous mutagens and genetic predisposition. IGF-I is a potent antiapoptotic factor for many cell types *(89),* and the hyperinsulinemia-induced increase in IGF-I bioactivity may promote the survival of transformed and abnormal cells that would normally undergo apoptosis. For example, data from an observational study *(90)* have shown that high levels of circulating IGF-I and enhanced genetic instability (increased mutagen sensitivity) are independently associated with an increased risk of lung cancer. The study also demonstrated an interaction between elevated IGF-I levels and the mutagen-sensitivity phenotype, suggesting that there may be a synergistic effect between these two factors and risk of lung cancer. The finding that orthotopically transplanted adenocarcinoma tissue shows decreased tumor growth and development in the hepatic IGF-I gene deletion mouse model of reduced circulating IGF-I concentrations *(64)* also supports this mechanism.

Thus, long-term exposure to increased IGF-I, with its mitogenic and antiapoptotic effects, may promote cancer development and progression at various stages of the carcinogenic process *(91).* In this scenario, short-term changes in IGF-I bioavailability are unlikely to play an important role in carcinogenesis, because the probability of transformed cells developing into cancer cells may be much lower with short, transient changes in IGF-I bioavailability than with more sustained changes. In addition, so far as we are aware, because no experimental studies have directly assessed this hypothesis, it is unclear as to whether IGF-I is also involved in *de novo* carcinogenesis.

Indirect Epidemiologic Data

The direct epidemiologic evidence for the role of insulin, IGF-I, and IGFBPs in colorectal carcinogenesis is also consistent with more inferential data. Possible anthropometric markers of hyperinsulinemia, such as waist circumference, waist-to-hip ratio, and body mass index, have been positively associated with risk of colorectal cancer *(2,5,11).* Height is also positively related to risk of colorectal cancer *(2)* and may, to some extent, reflect adolescent IGF-I levels, which correlate modestly with

height *(92,93)*. High levels of physical activity have been consistently associated with a decreased risk of colorectal cancer *(94)*. This relationship might be due to the association of physical activity—especially in individuals with lower body mass—with lower fasting and postprandial serum insulin concentrations *(95)*.

Limitations of the Model

The precise relationship among hyperinsulinemia, IGF-I bioavailability, and risk of colorectal cancer is not yet clear. Part of this uncertainty is due to the complex interactions among physical activity, body size, nutrition status, and energy intake, all of which may directly influence circulating concentrations of insulin, IGF-I, and IGFBPs and, therefore, the risk of colorectal cancer *(2,91,94,95)*. These and other associated risk factors may modify or confound the relationship between IGF-I and risk of colorectal cancer. Thus, whether known risk factors for colorectal cancer act through changes in insulin, IGF-I, and IGFBPs or, alternatively, through biologic mechanisms independent of the molecules in this pathway, remains to be resolved. Moreover, the biologic interactions among insulin, IGF-I, and IGFBPs may themselves be markers of other possible risk factors for colorectal cancer.

Recent studies *(73,96)* also suggest that inter-individual variability in concentrations of IGF-I and its binding proteins may be partly the result of genetic differences. At least two studies *(65,66)* have shown that polymorphic variations in the GH or IGF-I gene are associated with both serum IGF-I concentrations and chronic disease risk, including risk of colorectal cancer and adenoma. A study of twins *(35)* also indicates that variability in circulating IGF-I levels may have a heritable component; hence, it is possible that genetic factors and epigenetic processes that determine circulating concentrations of IGF-I and IGFBPs may interact to influence colorectal cancer risk. Thus, individuals with genetically determined elevated circulating IGF-I concentrations, who also have increased IGF-I bioavailability as a result of increased serum insulin concentrations, may have an elevated risk of colorectal cancer compared with individuals with relatively low insulin and IGF-I levels.

Alternatively, because tumors may themselves be a source of IGF-I, the reported associations among IGF-I, IGFBPs, and risk of colorectal cancer could be the result of undiagnosed cancer. The four prospective studies *(5,22,23,45)* that assessed the relationship between IGF-I levels and risk of colorectal cancer had between 6 and 14 years of follow-up, whereas the latency period between initiation and progression to symptomatic colorectal cancer may be more than 10 years. Indeed, one study *(45)* found an increased risk for IGF-II and IGFBP-3 only for cases diagnosed within 8 years of baseline assessment of serum IGF concentrations.

However, another study *(23)* found that the association between IGF-I and colorectal cancer was stronger for participants with longer follow-up, suggesting that the association was not due to undiagnosed cancer (because with such an association, an attenuation of the effect would be expected with longer follow-up). Furthermore, the positive association between the incidence of colorectal adenomas and circulating IGF-I levels also suggests that the association is unlikely to be due to undiagnosed carcinoma *(22)*. More persuasive evidence comes from genetic association studies. As already noted, polymorphic variation in the growth hormone gene, GH1, was associated with both circulating IGF-I concentrations and risk of colorectal cancer, suggesting that lifetime exposure may be an important determinant of risk *(66)*.

Preventive and Therapeutic Strategies

If insulin, IGF-I, and IGFBPs turn out to be important regulators of colorectal carcinogenesis, it will be important to determine how genetic and environmental factors influence intra- and inter-individual variations in IGF-I concentrations and bioavailability *(97)*. A clearer understanding of the mechanisms that determine IGF-I bioavailability may provide opportunities for cancer prevention and control, including nutritional and pharmacologic interventions. From a population and preventive perspective, it appears that modifying insulin levels by reducing obesity, changing diet, and increasing physical activity may be the most effective strategy for reducing levels of bioavailable IGF-I *(4,24,26,76)*.

From a therapeutic viewpoint, one study *(98)* has shown that octreotide, a somatostatin analogue, reduces circulating IGF-I levels and tumor cell proliferation in patients with newly diagnosed colon cancer. However, controlled trials of this drug in patients with advanced colon cancer have yielded inconsistent results, with one study *(99)* finding longer median survival times and increased disease stability and another study *(100)* finding no benefit. A more targeted approach to modulating IGF-I bioactivity, i.e., using more specific antagonists, may be more effective.

However, any approach that reduces IGF-I bioavailability has the possibility of substantial adverse side effects, primarily because IGF-I is an important component of other physiologic systems. Indeed, it has been suggested that IGF-I may be an important therapeutic agent for conditions such as type 1 and possibly type 2 diabetes, osteoporosis, protein metabolism in critically ill patients, disease-induced catabolic states, and age-associated tissue degeneration *(101–105)*. Recently, a microsatellite polymorphism in the promotor region of the IGF-I gene that confers low serum IGF-I levels was found to be associated with an increased risk of type 2 diabetes and myocardial infarction *(65)*. Therefore, attempts to influence IGF-I bioavailability in the context of colorectal cancer prevention will need to be considered in light of the possible effects on other chronic diseases *(106)*.

Suggestions for Future Research

Additional large-scale, longitudinal observational studies may help confirm the associations among serum concentrations of insulin, IGF-I, IGFBPs, and risk of colorectal cancer, particularly in relation to environmental and genetic determinants of IGF-I bioactivity and bioavailability. Cross-sectional and longitudinal observational studies, as well as experimental investigations, may also help clarify specific modifiable determinants and mediators of IGF-I concentrations and bioavailability.

Further characterization of polymorphisms in genes for IGF-I, the IGF-I receptor, IGFBPs, and their regulatory proteins, particularly those that are predicted to change protein structure, may provide more precise assessments of local IGF-I tissue production, bioactivity, and the effects of long-term exposure.

The existence of variants of genes encoding insulin and its receptor, and of intracellular signaling proteins that transduce signals from both IGF-I and insulin receptors *(54–57,107,108)*, may also help explain the intracellular processes underlying cel-

lular growth and proliferation, as will a better understanding of interactions of IGF-I receptor signaling pathways with other intracellular signaling mechanisms in carcinogenesis *(109)*.

As noted earlier, transgenic mice have been created that show a 75% reduction in circulating IGF-I levels *(32,64)*. Variants of this transgenic model, with more subtle changes in IGF-I levels, may be particularly useful in assessing the role of circulating IGF-I levels that are within the normal physiologic range in the development of colorectal cancer. Transgenic animals that overexpress IGF-I and IGFBPs could also be used in this context *(110,111)*.

Conclusion

IGF-I plays a critical role in cellular survival and proliferation. Recent evidence from both experimental and observational studies, including gene association investigations, suggests that it may also be important in the processes underlying carcinogenesis. Specifically, elevated circulating IGF-I concentrations have been associated with an increased risk of colorectal cancer. Furthermore, data from physiologic and clinical studies indicate that insulin may be an important mediator of IGF-I bioavailability, with insulin being positively related to IGF-I bioavailability. This new evidence for the biologic interactions among insulin, IGF-I, and its binding proteins in the context of colorectal carcinogenesis provides a potential mechanism through which previously identified diet and associated lifestyle factors may increase the risk of this cancer.

References

(1) World Health Organization (WHO). The World Health Report. Geneva (Switzerland): WHO; 1997.

(2) World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): WCRF/AICR; 1997.

(3) Lichtenstein P, Holm NV, Verkasalo PK, Iliadaou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85.

(4) Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995; 6:164–79.

(5) Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, et al. Serum C-peptide, IGF-I, IGFBPs, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–600.

(6) Reaven GM. The fourth Musketeer—from Alexandre Dumas to Claude Bernard. Diabetologia 1995;38:3–13.

(7) Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, et al. Prospective study of adult onset diabetes mellitus and risk of colorectal cancer in women. J Natl Cancer Inst 1999;91:542–7.

(8) Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998;147:816–25.

(9) Nishii T, Kono S, Abe H, Eguchi H, Shimazaki K, Hatano B, et al. Glucose intolerance, plasma insulin levels, and colon adenomas in Japanese men. Jpn J Cancer Res 2001;92:836–40.

(10) McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 1994;3:687–95.

(11) Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–54.

(12) Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H, et al. Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. Int J Epidemiol 1998;27:794–8.

(13) Koohestani N, Tran TT, Lee W, Wolever TMS, Bruce WR. Insulin resistance and promotion of aberrant crypt foci in the colon of rats fed on a high-fat diet. Nutr Cancer 1997;29:69–70.

(14) Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5:1013–15.

(15) Corpet DE, Jacquinet C, Peiffer G, Tache S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. Nutr Cancer 1997;27: 316–20.

(16) Koohestani N, Chia MC, Pham NA, Tran TT, Minkin S, Wolever TM, et al. Aberrant crypt focus promotion and glucose intolerance: correlation in the rat across diets differing in fat, n-3 fatty acids and energy. Carcinogenesis 1998;19:1679–84.

(17) Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 1989;80:51–8.

(18) Watkins LF, Lewis LR, Levine AE. Characterization of the synergistic effects of insulin and transferrin and the regulation of their receptors on a human colon carcinoma cell line. Int J Cancer 1990;45:372–5.

(19) Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000;21:215–44.

(20) Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological functions. Endocr Rev 1995;16:3–34.

(21) Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomarkers Prev 2000;9: 1271–9.

(22) Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and the risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9:345–49.

(23) Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens C, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF binding protein-3. J Natl Cancer Inst 1999;91:620–5.

(24) Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev 1994;15:80–101.

(25) Cohick WS, Clemmons DR. The insulin-like growth factors. Annu Rev Physiol 1993;55:131–53.

(26) Rajaram S, Baylink DJ, Mohan S. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocr Rev 1997;18:801–31.

(27) LeRoith D, Baserga R, Helman L, Roberts CT Jr. Insulin-like growth factors and cancer. Ann Intern Med 1995;122:54–9.

(28) Baserga R. The insulin growth factor I receptor: a key to tumour growth? Cancer Res 1995;55:249–52.

(29) Singh P, Rubin R. Insulin-like growth factors and binding proteins in colon cancer. Gastroenterology 1993;105:1218–37.

(30) Tricoli JV, Rall LB, Karakousis CP, Herrara L, Petrelli NJ, Bell GI, et al. Enhanced levels of insulin-like growth factor mRNA in human colon carcinomas and liposarcomas. Cancer Res 1986;46:6169–73.

(31) Kadowaki T, Tobe K, Honda-Yamamoto R, Tamemoto H, Kaburagi Y, Momomura K, et al. Signal transduction mechanism of insulin and insulin-like growth factor-1. Endocr J 1996;43 Suppl:S33–41.

(32) Yakar S, Liu JL, Stannard B, Butler A, Accili D, Sauer B, et al. Normal growth and development in the absence of hepatic insulin-like growth factor I. Proc Natl Acad Sci U S A 1999;96:7324–9.

(33) Underwood LE, Thissen JP, Lemozy S, Keteslegers JM, Clemmons DR. Hormonal and nutritional regulation of IGF-I and its binding proteins. Horm Res 1994;42:145–51.

(34) Hong Y, Pedersen NL, Brismar K, Hall K, de Faire U. Quantitative genetic analyses of insulin-like growth factor-I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. J Clin Endocrinol Metab 1996;81:1791–7.

(35) Hong Y, Brismar K, Hall K, Pedersen NL, de Faire U. Associations between insulin-like growth factor-I (IGF-I), IGF-binding protein-1, insulin and other metabolic measures after controlling for genetic influences: results from middle-aged and elderly monozygotic twins. J Endocrinol 1997;153:251–7.

(36) Ferry RJ Jr, Cerri RW, Cohen P. Insulin-like growth factor binding proteins: new proteins, new functions. Horm Res 1999;51:53–67.

(37) Jenkins PJ, Besser GM, Fairclough PD. Colorectal neoplasia in acromegaly. Gut 1999;44:585–7.

(38) Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and can-

cer incidence in acromegaly: a retropsective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 1998;83:2730–4.
(39) Cats A, Dullaart RP, Kleibeuker JH, Kuipers F, Sluiter WJ, Hardonk MJ, et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 1996;56:523–6.
(40) Jenkins PJ, Frajese V, Jones AM, Camacho-Hubner C, Lowe DG, Fairclough PD, et al. Insulin-like growth factor-I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 2000;85: 3218–21.
(41) Maison P, Balkau B, Simon D, Chanson P, Rosselin G, Eschwege E. Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study. BMJ 1998;316:1132–3.
(42) Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkebaek NE. The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. Clin Endocrinol (Oxf) 1994;41:85–93.
(43) Ghigo E, Aimaretti G, Maccario M, Fanciulli G, Arvat E, Minuto F, et al. Dose-response study of GH effects on circulating IGF-I and IGFBP-3 levels in healthy young men and women. Am J Physiol 1999;276: E1009–13.
(44) Yakar S, Liu JL, Fernandez AM, Wu Y, Schally AV, Frystyk J, et al. Liver-specific igf-1 gene deletion leads to muscle insulin insensitivity. Diabetes 2001;50:1110–8.
(45) Probst-Hensch NM, Yuan JM, Stanczyk FZ, Gao YT, Ross RK, Yu MC. IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. Br J Cancer 2001;85:1695–9.
(46) Kaaks R, Rinaldi S, Lukanova A, Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Correspondence re: Giovannucci et al., a prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomark Prev, 9: 345–349, 2000. Cancer Epidemiol Biomarkers Prev 2001;10:1103–4.
(47) Clemmons DR, Moses AC, McKay MJ, Sommer A, Rosen DM, Ruckle J. The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for *in vivo* biological activity. J Clin Endocrinol Metab 2000;85:1518–24.
(48) Murphy LJ, Molnar P, Lu X, Huang H. Expression of human insulin-like growth factor-binding protein-3 in transgenic mice. J Mol Endocrinol 1995;15:293–303.
(49) Pollak MN, Perdue JF, Margolese RG, Baer K, Richard M. Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer Lett 1987;38:223–30.
(50) Guo YS, Narayan S, Yallampalli C, Singh P. Characterization of insulin-like growth factor I receptors in human colon cancer. Gastroenterology 1992;102(4 Pt 1):1101.
(51) Freier S, Weiss O, Eran M, Flyvbjerg A, Dahan R, Nephesh I, et al. Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Gut 1999;44:704–8.
(52) Lahm H, Suardet L, Laurent PL, Fischer JR, Ceyhan A, Givel JC, et al. Growth regulation and co-stimulation of human colorectal cancer cell lines by insulin-like growth factor I, II and transforming growth factor alpha. Br J Cancer 1992;65:341–6.
(53) Lahm H, Amstad P, Wyniger J, Yilmaz A, Fischer JR, Schreyer M, et al. Blockade of the insulin-like growth factor-I receptor inhibits growth of human colorectal cancer cells: evidence of a functional IGF-II-mediated atocrine loop. Int J Cancer 1994;58:452–9.
(54) Baserga R, Hongo A, Rubini M, Prisco M, Valentinis B. The IGF-I receptor in cell growth, transformation and apoptosis. Biochim Biophys Acta 1997;1332:F105–26.
(55) Lopaczynski W. Differential regulation of signaling pathways for insulin and insulin-like growth factor I. Acta Biochim Pol 1999;46:51–60.
(56) Butler AA, Yakar S, Gewolb IH, Karas M, Okubo Y, LeRoith D. Insulin-like growth factor-I receptor signal transduction: at the interface between physiology and cell biology. Comp Biochem Physiol B Biochem Mol Biol 1998;121:19–26.
(57) Jhun BH, Meinkoth JL, Leitner JW, Draznin B, Olefsky JM. Insulin and insulin-like growth factor-I signal transduction requires p21ras. J Biol Chem 1994;269:5699–704.
(58) Leitner JW, Kline T, Carel K, Goalstone M, Draznin B. Hyperinsulinemia potentiates activation of p21Ras by growth factors. Endocrinology 1997; 138:2211–4.
(59) Akagi Y, Liu W, Zebrowski B, Xie K, Ellis LM. Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I. Cancer Res 1998;58:4008–14.
(60) Williams AC, Collard TJ, Perks CM, Newcomb P, Moorghen M, Holly JM, et al. Increased p53-dependent apoptosis by the insulin-like growth factor binding protein IGFBP-3 in human colonic adenoma-derived cells. Cancer Res 2000;60:22–27.
(61) Dunn SE, Kari FW, French J, Leininger JR, Travlos G, Wilson R, et al. Dietary restriction reduces insulin-like growth factor-I levels, which modulates apoptosis, cell proliferation, and tumour progression in p53-deficient mice. Cancer Res 1997;57:4667–72.
(62) Kari FW, Dunn SE, French JE, Barrett JC. Roles of insulin-like growth factor-I in mediating the anti-carcinogenic effects of caloric restriction. J Nutr Health Aging 1999;3:92–101.
(63) Butler A, Blakesley A, Tsokos VA, Pouliki M, Wood TL, LeRoith D. Stimulation of tumour growth by recombinant human insulin-like growth factor-I is dependent on the dose and the level of IGF-I receptor expression. Cancer Res 1998;58:3021–7.
(64) Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res 2002;62:1030–5.
(65) Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, et al. A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. Diabetes 2001;50:637–42.
(66) Le Marchand L, Donlon T, Seifried A, Kaaks R, Rinaldi S, Wilkens LR. Association of a common polymorphism in the human GH1 gene with colorectal neoplasia. J Natl Cancer Inst 2002;94:454–60.
(67) Smith WJ, Underwood LE, Clemmons DR. Effects of caloric and protein restriction on insulin-like growth factor-I and insulin-like growth factor binding proteins in children and adults. J Clin Endocrinol Metab 1995; 80:443–9.
(68) Forbes GB, Brown MR, Welle SL, Underwood LE. Hormonal responses to overfeeding. Am J Clin Nutr 1989;49:608–11.
(69) Cotterill AM, Holly JM, Wass JA. The regulation of insulin-like growth factor binding protein (IGFBP)-1 during prolonged fasting. Clin Endocrinol (Oxf) 1993;39:357–62.
(70) Vicini JL, Buonomo FC, Veenhuizen JJ, Miller MA, Clemmons DR, Collier RJ. Nutritional balance and stage of lactation affect responses of insulin, insulin-like growth factors I and II, and insulin-like growth factor-binding protein 2 to somatotropin administration in dairy cows. J Nutr 1991;121:1656–64.
(71) Lee PD, Giudice LC, Conover CA, Powell DR. Insulin-like growth factor binding protein-1: recent findings and new directions. Proc Soc Exp Biol Med 1997;216:319–57.
(72) Frystyk J, Grofte T, Skjaerbaek C, Orskov H. The effect of oral glucose on serum free insulin-like growth factor-I and -II in healthy adults. J Clin Endocrinol Metab 1997;82:3124–7.
(73) Brismar K, Fernqvist-Forbes E, Wahren J, Hall K. Effect of insulin on the hepatic production of insulin-like growth factor binding protein-1, IGFBP-3, and IGF-I in IDDM. J Clin Endocrinol Metab 1994;79:872–8.
(74) Frystyk J, Delhanty PJ, Skjaerbaek C, Baxter RC. Changes in the circulating IGF system during short-term fasting and refeeding in rats. Am J Physiol 1999;277(2 Pt 1):E245–52.
(75) Levitt Katz LE, Satin-Smith MS, Collett-Solberg P, Thornton PS, Baker L, Stanley CA, et al. Insulin-like growth factor binding protein-1 levels in the diagnosis of hypoglycemia caused by hyperinsulinism. J Pediatr 1997; 131:193–9.
(76) Conover CA, Lee PD, Kanaley JA, Clarkson JT, Jensen MD. Insulin regulation of insulin-like growth factor binding protein-1 in obese and nonobese humans. J Clin Endocrinol Metab 1992;74:1355–60.
(77) Clemmons DR, Snyder DK, Busby WH Jr. Variables controlling the secretion of insulin-like growth factor binding protein-2 in normal human subjects. J Clin Endocrinol Metab 1991;73:727–33.
(78) Argente J, Caballo N, Barrios V, Munoz MT, Pozo J, Chowen JA, et al. Disturbances in the growth hormone–insulin-like growth factor axis in children and adolescents with different eating disorders. Horm Res 1997; 48:16–18.

(79) Counts DR, Gwirtsman H, Carlsson LM, Lesem M, Cutler GB Jr. The effect of anorexia nervosa and refeeding on growth hormone binding protein, the insulin-like growth factors and their binding proteins. J Clin Endocrinol Metab 1992;75:762–7.
(80) Strasser-Vogel B, Blum WF, Past R, Kessler U, Hoeflich A, Meiler B, et al. IGF-I and -II and binding proteins-1, -2, and -3 in children and adolescents with diabetes mellitus: correlation with metabolic control and height attainment. J Clin Endocrinol Metab 1995;80:1207–13.
(81) Nam SY, Lee EJ, Kim KR, Cha BS, Song YD, Lim SK, et al. Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord 1997;21:355–9.
(82) Baxter RC. Insulin-like growth factor binding proteins as glucoregulators. Metabolism 1995;44:12–17.
(83) Frystyk J, Hussain M, Skjaerbaek C, Schmitz O, Christiansen JS, Froesch ER, et al. Serum free IGF-I during a hyperinsulinemic clamp following 3 days of admininistration of IGF-I vs. saline. Am J Physiol 1997;273(3 Pt 1):E507–13.
(84) Argente J, Caballo N, Barrios V, Munoz MT, Pozo J, Chowen JA, et al. Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in prepubertal children with exogenous obesity: effect of short- and long-term weight reduction. J Clin Endocrinol Metab 1997; 82:2076–83.
(85) Frystyk J, Skjaerbaek C, Vestbo E, Fisker S, Orskov H. Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes. Diabetes Metab Res Rev 1999;15:314–22.
(86) Chapman IM, Hartman ML, Pieper KS, Skiles EH, Pezzoli SS, Hintz RL. Recovery of growth hormone release from suppression by exogenous insulin-like growth factor I (IGF-I): evidence for a suppressive action of free rather than bound IGF-I. J Clin Endocrinol Metab 1998;83:2836–42.
(87) Attia N, Caprio S, Jones TW, Heptulla R, Holcombe J, Silver D, et al. Changes in free insulin-like growth factor-1 and leptin concentrations during acute metabolic decompensation in insulin withdrawn patients with type 1 diabetes. J Clin Endocrinol Metab 1999;84:2324–8.
(88) Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
(89) Grimberg A, Cohen P. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. J Cell Physiol 2000; 183:1–9.
(90) Wu X, Yu H, Amos CI, Hong WK, Spitz MR. Joint effect of insulin-like growth factors and mutagen sensitivity in lung cancer risk. J Natl Cancer Inst 2000;92:737–43.
(91) Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000;92:1472–89.
(92) Gunnell D. Height, insulin-like growth factors and cancer risk. Growth Hormone IGF Res 2000;10 Suppl A:S39–40.
(93) Giovannucci E. Insulin-like growth factor-I and binding protein-3 and risk of cancer. Horm Res 1999;51:34–41.
(94) Slattery ML, Potter J, Caan B, Edwards S, Coates A, Ma KN, et al. Energy balance and colon cancer—beyond physical activity. Cancer Res 1997; 57:75–80.
(95) Kaaks R, Lukonova A. Energy balance and cancer: the role of insulin and insulin growth factor-I. Proc Nutr Soc 2001;60:91–106.
(96) Deal C, Ma J, Wilkin F, Paquette J, Rozen F, Ge B, et al. Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators. J Clin Endocrinol Metab 2001;86:1274–80.
(97) Ma J, Giovannucci E, Pollak M, Chan JM, Gaziano JM, Willett W, et al. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J Natl Cancer Inst 2001;93:1330–6.
(98) Cascinu S, Ferro ED, Grinati C, Ligi M, Ghiselli R, Foglietti G, et al. Inhibition of tumour cell kinetics and serum IGF-I levels by octreotide in colorectal cancer patients. Gastroenterology 1997;113:767–72.
(99) Cascinu S, Del Ferro E, Catalano G. A randomized trial of octreotide vs best supportive care only in advanced gastrointestinal cancer patients refractory to chemotherapy. Br J Cancer 1995;71:97–101.
(100) Goldberg RM, Moertel CG, Wieand HS, Krook JE, Schutt AJ, Veeder MH, et al. A phase III evaluation of a somatostatin analogue (octreotide) in the treatment of patients with asymptomatic advanced colon carcinoma. Cancer 1995;76:961–6.
(101) Dunger DB, Acerini CL. Does recombinant human insulin-like growth factor have a role in the treatment of diabetes? Diabetic Med 1997;14: 723–31.
(102) Gelato MC. The growth hormone/insulin-like growth factor axis in critical illness. J Pediatr Endocrinol Metab 2000;13:1023–9.
(103) Ross RJ. GH, IGF-I and binding proteins in altered nutritional states. Int J Obes Relat Metab Disord 2000;24 Suppl 2:S92–5.
(104) Borst SE, Lowenthal DT. Role of IGF-I in muscular atrophy of aging. Endocrine 1997;7:61–3.
(105) Ohlsson C, Bengsston BA, Isaksson OG, Andreassen TT, Slootweg MC. Growth hormone and bone. Endocr Rev 1998;19:55–79.
(106) Burroughs KD, Dunn SE, Barrett JC, Taylor JA. Insulin-like growth factor-I: a key regulator of human cancer risk? J Natl Cancer Inst 1999; 91:579–81.
(107) Stumvoll M, Fritsche A, Volk A, Stefan N, Madaus A, Maerker E, et al. The Gly972Arg polymorphism in the insulin receptor substrate-1 gene contributes to the variation in insulin secretion in normal glucose-tolerant humans. Diabetes 2001;50:882–5.
(108) Withers DJ, Burks DJ, Towery HH, Altamuro SL, Flint CL, White MF. IRS-2 coordinates IGF-I receptor-mediated beta-cell development and peripheral insulin signalling. Nat Genet 1999;23:32–40.
(109) Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature 2001; 411:355–65.
(110) Modric T, Silha JV, Shi Z, Gui Y, Suwanichkul A, Durham SK, et al. Phenotypic manifestations of insulin-like growth factor-binding protein-3 overexpression in transgenic mice. Endocrinology 2001;142:1958–67.
(111) Schneider MR, Lahm H, Wu M, Hoeflich A, Wolf E. Transgenic mouse models for studying the functions of insulin-like growth factor-binding proteins. FASEB J 2000;14:629–40.

NOTES

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