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Cancer

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1. Introduction

The growth hormone (GH)/insulin-like growth factor (IGF) axis is the principal endocrine system controlling somatic growth. Hormones are defined as molecules that are released by endocrine glands into the circulation for delivery to target tissues, where they exert their effects via specific receptor binding and post-receptor signaling. Hence, endocrinologists have traditionally measured circulating hormone levels as a major marker of endocrine system action. Epidemiologic data have associated cancer risk with changes in circulating levels of several GH/IGF axis components. The reproducibility of these findings has focused a lot of attention recently on the possible role the GH/IGF axis may contribute to cancer development and progression.

There are two important shortcomings with this approach. First, associations can never prove causation, because the direction of causation remains unknown and there may be confounders. Second, as unexpectedly demonstrated by liver-specific *igf1* gene-deleted (LID) mice, endocrine IGF is but part of the story. Despite a 75% reduction in circulating IGF-I concentrations, LID mice had normal postnatal growth¹. Just as the relative contributions of endocrine versus local (autocrine or paracrine) GH/IGF axis components are being questioned in normal growth, so too is their significance in the neoplastic process.

Thus, there are two levels of possible GH/IGF contributions, each supported by different types of data. Endocrine action is investigated in epidemiologic studies and some *in vivo* animal tumor models, whereas autocrine/paracrine actions are studied in *in vitro* experiments of cellular signaling and some *in vivo* animal models. The relative significance of and the relationships between these two levels in carcinogenesis remain unclear, but data are accumulating for both. Currently, there is no strong evidence that GH or IGF-I causes cancer, but the data suggest a possible promoting role for preexisting lesions.

2. Endocrine GH/IGF Axis

2.1 GH

Epidemiologic data associating circulating GH levels with cancer risk have come from various patient populations, which serve as human models of high or low GH levels, and

more recently, variations within the normal population. Animal models have also contributed to this field.

2.1.1 GH Deficiency—Concern for a possible carcinogenic effect of GH was raised in 1988 by a letter to *Lancet*, in which the authors reported a higher incidence of leukemia in their GH recipients than children of the general population². Subsequent reanalyses identified the greater presence of leukemic risk factors, such as prior neoplasms and radiation therapy, among GH-deficient children as a confounder^{3,4}. Many patients on recombinant human GH (rhGH) therapy are enrolled in post-marketing surveillance studies, including the National Cooperative Growth Study, KABI International Growth Study, and others, which serve as powerful research tools that complement the safety monitoring by the Food and Drug Administration's MED WATCH system. A review of 12,209 patients in one such study, representing more than 51,000 patient-years at risk, revealed 10 new cases of extracranial neoplasms, which did not differ from the expected incidence derived from the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) Program⁵. Additional data are continuously being accumulated, and the current tally exceeds 200,000 patient-years at risk.

A recent retrospective cohort study renewed the scare following years of reassuring experience. In the United Kingdom, 1848 patients treated with cadaveric pituitary-derived GH from 1959 to 1985, were followed up for cancer incidence through 1995 and mortality through 2000. The authors found a higher incidence of colorectal cancer ($n = 2$) and higher rates of mortality from colorectal cancer ($n = 2$) and Hodgkin's disease ($n = 2$) compared to the general population⁶. The small numbers make inference difficult, as does the switch from cadaveric pituitary-derived GH to rhGH in 1985. Implications for clinical rhGH therapy will be addressed in Section 16.5.1, but this study certainly underscores the need for long-term surveillance of GH recipients into adulthood, when the incidence of cancer normally rises.

Regarding untreated GH deficiency, a retrospective review of 333 patients consecutively diagnosed between 1956 and 1987 revealed 3 male deaths from malignancy (expected 10.1) and 4 female deaths (expected 4.1)⁷. But the major finding of this study was a shortened life expectancy, associated with an increased mortality from cardiovascular disease.

2.1.2 Acromegaly—Acromegaly, a condition of pathologic GH excess most commonly caused by a GH-secreting pituitary adenoma, has been studied as a natural model of GH effects on carcinogenesis. Because the underlying pituitary tumor is benign (adenoma), and stereotactic radiation therapy is reserved for surgery- and medication-resistant cases, changes in cancer development in these patients are generally related to the GH excess. The conclusions are controversial (for an excellent point/counterpoint, see ref. 8 and 9), for two main reasons. First, acromegaly is rare (prevalence of 4 to 6 per million), so many studies are uncontrolled, retrospective, small series reports. It is difficult to accurately determine the true cancer incidence among acromegalics from such data, and ascertainment bias may be affecting the results. Second, prior to therapeutic advances, premature mortality (primarily from cardiovascular disease) prevented acromegalic individuals from reaching older ages, when cancer risk is greatest. Thus, meta-analyses comparing early versus more recent

reports may show different results, and the appropriateness of the selected control populations may be questionable. By virtue of dying younger than the control population, the acromegalic cancer risk may be under-appreciated. To resolve the debate, multicenter acromegaly registries are being compiled in the United States and United Kingdom.

Data thus far suggest, if anything, an effect of acromegaly on colorectal neoplasia. Still, findings of an increased incidence of colon polyps and adenocarcinoma have been inconsistent^{8,9}. Again, experimental design issues, including control reference data and examination techniques (flexible sigmoidoscopy versus full-length colonoscopy), may be confounding the analyses. It is generally agreed that colorectal neoplasia behaves differently in this patient group. Acromegalics have increased length of total colon and sigmoid loop, mucosal hypertrophy, prolonged colon transit times, and higher levels of deoxycholic acid reflecting increased transit times and intraluminal bacterial activity^{10,11}. In acromegalics, colonic lesions tend to be more right-sided, adenomas tend to be larger and more dysplastic, and polyps more often occur multiply¹².

Colon cancer in acromegaly is an excellent example of how epidemiologic associations are insufficient to prove causation. Acromegaly is the clinical model of GH excess. Yet IGF-I is also pathologically increased in acromegaly. So is it the GH or the IGF-I? Intestinal length and mucosal mass were increased in transgenic mice that overexpressed either GH and IGF-I or IGF-I alone (with GH suppression); increased crypt cell proliferation was observed only in the IGF-I transgenics, whereas GH excess stimulated more intestinal epithelial cell differentiation¹³⁻¹⁶. Furthermore, does the IGF-I excess promote colon cancer directly, through the mechanisms described later in this chapter, or is there a confounder? For instance, excessive IGF-I may lead to increased intestinal length, which prolongs transit time and thereby leads to greater deoxycholic acid levels¹⁷. Deoxycholic acid has been implicated in colonic mucosal proliferation¹⁸ and colon cancer cell migration¹⁹, and has been shown to stimulate proteasomal degradation of the tumor suppressor p53²⁰ and at high concentrations, inhibit expression of the tumor suppressor *BRCA1*²¹.

The possibility of confounding has been similarly raised for prostate cancer in acromegaly. Accentuated and early benign prostatic hyperplasia has been reported in acromegaly²². This may lead to an ascertainment bias, as these men may be more likely to seek medical attention for prostate-related symptomatology and be more likely to have detection of subclinical prostate cancer²³. The overall association of acromegaly with prostate cancer risk is still unclear, owing to the aforementioned effects of early mortality on study results. Thus, we await the outcomes of the multicenter acromegaly registries and additional mechanistic studies.

2.1.3 Normal GH Variability—Recently, the consequences of subtle variations in circulating hormone levels within the normal population, rather than larger pathologic changes, have become the interest of epidemiologic studies. A T-to-A polymorphism at position 1663 of the human *GHI* gene has been identified as a cause of such variability in GH and IGF-I levels. Data from two case-control studies in Hawaii are summarized in Table 1. The first was a population-based study of 535 case patients with colorectal adenocarcinoma and 650 control subjects; the second, a sigmoidoscopy screening-based

study of 139 case patients with adenoma and 202 control subjects²⁴. They showed that the A allele was associated with a lower ratio of plasma IGF-I/IGFBP-3 and a lower risk of colorectal cancer in the total population; the reduction in colorectal cancer risk was evident in the Caucasian and Native Hawaiian subgroups of the population, but not in the Japanese. Thus, additional ethnic genetic and/or environmental factors, such as diet or exercise, can modify the effects of GH variability on cancer risk.

2.1.4 Animal Models—Animal models allow independent manipulation of both hormonal levels and environmental factors such as carcinogen exposure to test relationships between the two. Mammary carcinogenesis was studied in Spontaneous Dwarf rats (SDR), which are Sprague Dawley rats rendered GH deficient by a *GH* gene mutation²⁵. When exposed to the direct-acting carcinogen *N*-methyl-*N*-nitrosourea, SDR exhibited lower mammary tumor incidence (3 of 15 rats) and lower tumor number (average 0.2 tumors/rat) compared to similarly exposed wild-type rats (10 of 10 rats and 5.3 tumors/rat, respectively). The indirect-acting carcinogen 7,12-dimethylbenz[*a*] anthracene (DMBA) produced an average 0.21 tumors per SDR/SDR rat versus 4 tumors per wild type or heterozygous rat. Yet these rats also demonstrated an important role for GH in normal mammary gland development. SDRs had less alveolar development, but normal ductal branching; GH infusion induced epithelial cell proliferation and alveolar development similar to that of the wild-type rats.

Mammary carcinogenesis was also studied in dwarf rats (*dw*) of the Lewis strain, who harbor a recessive mutation specifically affecting GH synthesis²⁶. Heterozygous *dw*/+ rats are normal size; homozygous *dw*/*dw* rats have 10% circulating GH concentrations and 50% IGF-I concentrations of their heterozygous littermates. *dw*/*dw* and their *dw*/+ littermates were treated with DMBA on day of life 50 and then 6 weeks of daily injections: *dw*/+ received normal saline, whereas the *dw*/*dw* rats were randomized among saline and low- and high-dose porcine GH. None of the *dw*/*dw* saline rats developed mammary tumors by 27 weeks after DMBA; 70% of *dw*/+ rats had tumors. GH treatment dose-dependently increased mammary tumorigenesis in the *dw*/*dw* rats (83% of low-dose and 100% of high-dose). These studies indicate the GH/IGF-I deficiency confers resistance to carcinogen-induced tumor formation.

2.2 IGF-I

2.2.1 Epidemiologic Studies—Multiple large case-control studies have found positive associations between high circulating IGF-I concentrations and increased risk for different types of cancer. The striking features of these studies are the reproducibility across cancer types and the significant effects of variations in IGF-I concentrations that fall within the normal range, *i.e.* the “high” IGF-I levels in these studies are not pathologically high from disease states, but rather the highest quartile or quintile of the general population compared to the lowest quartile or quintile. These studies are extensively discussed elsewhere^{23,27}, and summarized in Table 2²⁸⁻⁵⁰.

2.2.2 Animal Models—As described in the introduction, LID mice serve as the classic model to distinguish endocrine from autocrine/paracrine IGF-I, and have circulating IGF-I concentrations 25% of normal¹. Six weeks of treatment with recombinant human IGF-I or

saline further manipulated the circulating IGF-I concentrations such that control + IGF-I had the highest IGF-I levels, LID + saline had the lowest, and control + saline and LID + IGF-I fell inbetween. When mouse colon adenocarcinoma cells were transplanted onto the surface of the cecum of these animals, the aggressiveness of tumor behavior paralleled the IGF-I levels. Control + IGF-I mice had the greatest frequency of tumor growth, greatest mean tumor weight, greatest tumor vessel count, greatest frequency of hepatic metastases, and greatest numbers of metastases per liver; LID + saline mice had the lowest by all parameters, and the other mice were intermediary⁵¹.

Athymic nude mice were injected with fibroblasts that contained either normal (16,000/cell) or experimentally increased (190,000/cell) density of the type 1 IGF receptor (IGF-1R). Systemic IGF-I treatment did not change tumor development in the mice injected with normal fibroblasts. However, for the mice with high IGF-1R fibroblasts, systemic IGF-I treatment decreased tumor latency, increased fibrosarcoma growth, and increased mitogenesis⁵².

Circulating IGF-I had an effect on cancer behavior in both models, but it is important to note that both also involved local changes in the cell's growth regulatory mechanisms (preexisting adenocarcinoma or almost 12-fold over-expression of IGF-1R). Thus, the current evidence may support a permissive effect of circulating IGF-I on existing cancers, but not a causal role in the creation of cancer.

2.3 IGFBP-3

Many of the same case-control studies showing positive associations of cancer risk with high IGF-I concentrations showed inverse associations of cancer risk with high IGFBP-3 concentrations. This suggests that theoretically the greatest risk of developing cancer comes from having high IGF-I coupled with low IGFBP-3 levels. GH raises both. The IGFBP-3 data are also summarized in Table 2²⁸⁻⁵⁰.

3. Autocrine/Paracrine GH/IGF Axis

Many studies have demonstrated that local perturbations in the GH/IGF axis can enhance cell survival and proliferation, and thereby promote cancer. These changes can occur in the cancerous cell itself or in the supporting stroma. Several caveats must be kept in mind. Foremost, multiple genetic changes are required for the creation and progression of each and every cancer, so the GH/IGF axis must be considered within that greater context. Second, none of the changes are universal; they are frequently cancer type-specific and even within a cancer type, stage-specific. Finally, an exhaustive review of all the published changes would exceed the scope of this chapter. What follows, then, is a selective review of illustrative examples demonstrating pathophysiologic principles by which GH/IGF axis changes may contribute to cancer.

3.1 GH

Although the pituitary gland is the main source of GH in the body, abnormal augmentation of local GH production can increase proliferation of the local cells. For example, expression of GH mRNA identical to pituitary GH mRNA has been shown in the ductal luminal

epithelial and myoepithelial cells and scattered stromal fibroblasts of normal human mammary glands. This expression was increased in both the epithelial and supporting stromal compartments of three progressive proliferative disorders: benign fibroadenoma, preinvasive intraductal carcinoma, and invasive ductal carcinoma with lymph node metastases⁵³. Normal, proliferative, and neoplastic lesions of the breast were also found to express the GH receptor (GHR), as did the stroma to a lesser degree. GHR expression levels varied greatly among individuals, but did not correlate with lesion histology⁵⁴. When MCF-7 human breast cancer cells were stably transfected with either the gene for human GH or a translation-deficient mutated *GH* gene, GH expression increased cellular proliferation and was synergistic with trophic factors such as IGF-I⁵⁵. Mechanistically, GH caused transcriptional repression of the p53-regulated placental transforming growth factor- β (PTGF- β); reduced PTGF- β in turn led to decreased Smad-mediated transcription which resulted in decreased cell cycle arrest and apoptosis⁵⁵.

3.2 IGFs

Like GH, overexpression of the IGFs may enhance cell survival and proliferation. For example, IGF-I overexpression was found in 31 of 50 thyroid adenomas and 38 of 53 thyroid carcinomas examined, and correlated with carcinoma tumor diameter but not patient age, gender, or tumor stage⁵⁶. IGF-I was not increased in sporadic adrenocortical carcinomas, but the amount of IGF-II protein in the malignant tumors far exceeded that in benign tumors or normal adrenal tissue⁵⁷.

The single-copy six-exon *IGF-I* gene is transcribed from two promoters (P1 and P2), located 5' to exons 1 and 2, respectively, resulting in RNAs with different 5' leader sequences; alternative RNA splicing and differential polyadenylation yield multiple mature transcripts⁵⁸. Normally, local IGF-I expression can be increased by GH⁵⁹, estrogen⁶⁰, cAMP⁶¹, and transforming growth factor- β (TGF- β)⁶² and decreased by glucocorticoids⁶³. In contrast, the most common mechanism of IGF-II overexpression involves loss of imprinting; IGF-II is normally expressed from the paternal allele only and is under reciprocal regulation with the maternally expressed tumor suppressor, H19^{64,65}.

As proof of principle, two sets of IGF-I transgenic mice created by DiGiovanni *et al.* supported the hypothesis that local IGF-I overexpression can enhance cellular proliferation and contribute to neoplasia. Transgenic mice overexpressing IGF-I in the basal epithelial cells of the prostate developed prostatic hyperplasia by 2 to 3 months of age, and atypical hyperplasia and prostatic intraepithelial neoplasia by 6 to 7 months. Well-differentiated adenocarcinomas were found in mice starting at age 6 months, and two of the older mice developed less differentiated (small cell) carcinomas. Of all the mice aged 6 months or greater, 50% had prostate tumors⁶⁶. Transgenic mice overexpressing IGF-I in the basal cells of the epidermis had morphologic changes of their skin and ears, epidermal hyperplasia, hyperkeratosis, and about half the older mice developed squamous papillomas, some of which converted into carcinomas. Increased skin proliferation was indicated by increased labeling index. IGF-I overexpression also increased susceptibility to carcinogens, as carcinogen-induced papilloma development in the IGF over-expressing mice was seven fold greater than in their nontransgenic littermates⁶⁷.

3.3 IGF Receptors

Overexpression of the IGF receptor can also augment cellular proliferation, and when concomitant with IGF overexpression, forms an effective autocrine loop for self-stimulated growth. The growth-promoting actions of both IGF-I and IGF-II are mediated by the type 1 IGF receptor (IGF-1R), an $\alpha_2\beta_2$ heterotetrameric tyrosine kinase receptor closely related to the insulin receptor (IR). Not only are IGF-1R and IR structurally homologous, but they also share common signaling pathways, ligand cross-reactivity, and can form hybrid receptors. (Table 3)⁶⁸⁻⁷³.

Overexpression of IGF-1R, IR, and hybrid receptors have all been found in cancers, such as cancers of the breast⁷⁴ and thyroid⁷⁵. In fact, IGF-I-stimulated growth of thyroid papillary carcinoma cells in culture was attenuated by antibodies specifically targeting either IGF-1R or hybrid receptors⁷⁵. Thus, the hybrid receptors are not merely structural errors from receptor over-expression, but serve growth-promoting functions in the malignant cells.

3.4 IGF/Receptor Signaling

Ligand binding to the IGF-1R (and IR) causes autocatalytic phosphorylation of the receptor's tyrosine kinase domain, which also phosphorylates additional IGF-1R (and IR) tyrosine residues important for the recruitment of adapter molecules like IRS and Shc. These in turn activate kinase cascades, primarily the PI3 kinase/Akt (PKB) pathway and the MAP kinase pathway, respectively, and lead to signal transduction to the nucleus and mitochondrion⁷⁶.

Enhanced IGF/IGF-1R signaling can contribute to each of the four stages of cancer progression⁷⁶. In the first stage, malignant transformation, a cell must acquire the ability to both advantageously proliferate and escape the body's protective mechanisms, *i.e.* cell cycle arrests that regulate cell growth and apoptosis, or cell suicide, that aborts any aberrant cells. Stimulation by growth factors, like IGF-I, is required for cell cycle entry and progression to the late G₁ phase restriction point, beyond which the cell is committed to completing a round of cell division. IGF-I stimulates the G₁ phase progression by inducing cyclin D1 for assembly with cyclin-dependent kinase (CDK)^{477,78}. IGF-I can further stimulate survival and proliferation through multiple branch points of its signaling pathways, one of which is summarized here and in Figures 1 and 2. As shown in Figure 1, IGF-1R binding by IGF leads to phosphorylation and activation of Akt via PI3 kinase⁷⁹. Activated Akt, itself a kinase, phosphorylates multiple substrates including the Bcl-family member, Bad, and the forkhead transcription factor, FKHRL1. When phosphorylated, Bad and FKHRL1 are sequestered in the cytoplasm by binding to 14-3-3 proteins. Akt also phosphorylates caspase 9, directly inhibiting its function, and IKK α , thereby activating NF κ B for nuclear localization and transcriptional activation of survival genes such as *c-myc*. Conversely, the consequences of Akt inactivation, when IGF/IGF-1R signaling is absent, are shown in Figure 2. Unphosphorylated Bad localizes to the mitochondrion, where it binds Bcl-X_L and releases cytochrome *c* to the apoptosome, thereby activating caspase 9. Similarly, unphosphorylated FKHRL1 localizes to the nucleus, where it transcriptionally activates numerous genes including IGFBP-1 and FasL. FasL is the ligand (hence, the name) of Fas, the membrane-bound death receptor that activates caspase 8 via the adapter molecule,

FADD. Thus, both the mitochondrial and cytoplasmic caspase cascades are activated and converge on activating the execution caspases to complete apoptosis. In short, activation of Akt by IGF/IGF-1R accomplishes both, stimulating cell survival while avoiding apoptosis^{76,80,81}.

The second stage of cancer progression involves additional adaptations that enable continued growth of the clonally expanded, transformed cell as a bulky tumor, wherein nutrient delivery may become restrictive. As shown in colon^{82,83}, lung⁸⁴, and thyroid cancers⁸⁵, IGF-I induces the angiogenesis agent, vascular endothelial growth factor (VEGF), via increased synthesis of the HIF1 α transcription factor. Colon cancer cells harboring a dominant-negative truncated IGF-1R, when injected into nude mice, developed smaller tumors, reduced VEGF expression, lower tumor vessel count, and decreased pericyte coverage of endothelial cells⁸⁶.

IGF-1R signaling further contributes to cell motility and cell environment interactions that are important for local invasion and the metastatic process. Adherence junctions connect epithelial cells into a normally growing sheet and consist of a core (transmembrane E-cadherin plus cytoplasmic α -, β -, and γ -catenins) that is coupled to microfilaments via α -catenin, either directly or indirectly through α -actinin and vinculin⁸⁷. In MCF-7 breast cancer cells, IGF-1R signaling was shown to promote cell separation, via disassembly of the adherence junctions and redistribution of α -actinin, actin, and fascin into motile apicolateral spikes, as well as to cell migration, via reassembly of stress fibers, development of long membrane protrusions, and stimulation of myosin light chain kinase⁸⁸. IGF-1R signaling also relocalizes integrins to the leading edge of migrating cells. Conversely, integrins, heterodimers that bind extracellular matrix molecules and transduce signals to the intracellular environment, can modulate IGF-1R signaling when they are activated by their own ligand binding⁸⁹. While inducing cellular changes necessary for motility, IGF-1R signaling can help create a suitable microenvironment for the migrating cell by inducing expression of proteases like cathepsin D⁹⁰, matrix metalloproteinases^{91,92}, and urokinase plasminogen activator⁹³. These proteases not only dissolve basement membranes in the path of the migrating cell, but they can also cleave IGFBP-3, thereby releasing any bound IGF in the microenvironment for further cell stimulation⁹⁴. Transfection of IGF-1R increased cell spreading on fibronectin, colony formation in soft agar, and metastatic behavior of M-27 Lewis lung carcinoma cells, which are usually poorly invasive and express low numbers of IGF-1R; use of site-directed mutants enabled further delineation of the various IGF-1R functions to different subsets of the normal tyrosine phosphorylation sites⁹⁵.

During the last stage, many cancers acquire resistance to therapeutic agents designed to kill rapidly proliferating cells. Conditions of increased IGF signaling led to increased resistance of a variety of cancer cell lines to such agents in *in vitro* experiments. These include resistance of breast⁹⁶ and colorectal cancer⁹⁷ cells to irradiation; breast cancer cells to herceptin⁹⁸, doxorubicin, and taxol⁹⁹; colorectal cancer cells to 5-fluorouracil⁹⁷; small cell lung cancer cells to etoposide¹⁰⁰; pancreatic cancer cells to COX-2 inhibitors¹⁰¹; rhabdomyosarcoma cells to rapamycin¹⁰²; metastatic sarcoma cells to doxorubicin¹⁰³; leukemic cells to all-trans-retinoic acid (ATRA)¹⁰⁴; and multiple myeloma¹⁰⁵ and thyroid cancer cells¹⁰⁶ to Apo2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).

3.5 IGFBPs

Another major mechanism for enhanced cellular survival and proliferation is the reduction of IGFBPs, either through decreased expression or increased proteolysis. Because the binding affinity of IGF for the IGFBPs exceeds that for IGF-1R, IGFBPs tend to reduce IGF/IGF-1R signaling through competitive binding. This has been demonstrated by numerous experiments in different cell types using Des-(1-3)-IGF-I, an IGF-I analog that binds IGF-1R and stimulates DNA synthesis but cannot bind IGFBP-3¹⁰⁷⁻¹⁰⁹. As the principal endocrine IGFBP, IGFBP-3 is the best studied and will be the focus of this discussion.

In addition to inhibiting growth by preventing IGF from binding IGF-1R, IGFBP-3 can also inhibit growth and induce apoptosis in an IGF-independent manner⁶⁸. This has been demonstrated by experiments using IGF-free systems, *IGF-1R*^{-/-} cells and rhIGFBP-3 fragments with negligible binding affinity for IGF-I^{68, 110,111}. IGF-independent actions of IGFBP-3 are presumed to occur via IGFBP-3-specific receptors, which were first detected on the surface of breast cancer cells^{112,113} and involve the midregion of the IGFBP-3 molecule¹¹⁴. The exact signal transduction pathway of IGFBP-3-mediated apoptosis is still unclear, but proposed mechanisms include: direct inhibition of IGF-1R¹¹⁵, increased intracellular calcium¹¹⁶, nuclear translocation and RXR-binding^{117,120}, changes in Bcl family members¹²¹, and mitochondrial actions¹²².

Thus, a cell can increase its IGF bioavailability, enhance its growth and reduce apoptosis by decreasing the amount of IGFBP-3¹¹⁰. Changes in levels of the other IGFBPs, both up and down, have also been found in a variety of cancers, including prostate⁹⁴, lung¹²³, and adrenocortical tumors⁵⁷. Although generally thought to be growth inhibitory, IGFBPs have been shown to be growth stimulatory under certain experimental conditions. By sequestering IGF from the IGF-1R, the IGFBPs may allow local accumulation of IGF without down-regulation of the IGF-1R; when this local pool is simultaneously released through IGFBP proteolysis into low-affinity IGF-binding fragments, a greater amount of IGF can bind the IGF-1R for a larger growth stimulus than had the IGF accumulated in a bioavailable form all along⁸. Hence, the literature contains conflicting reports of increased IGFBP levels as growth inhibitory or growth stimulatory¹²⁴, and further studies are needed. The growth stimulatory effect of IGF presentation is illustrated in Figure 1, and the growth inhibition, via inhibition of IGF-1R signaling or via IGFBP-3-receptor-mediated pathways, is illustrated in Figure 2.

3.6 IGFBP Proteases

As mentioned, IGFBP proteases play a critical role in modulating the local bioavailability of IGF for binding IGF-1R; IGF binding affinity is greatest for the intact IGFBP, less for IGF-1R, and less still for IGFBP fragments. Prostate-specific antigen (PSA), whose serum level correlates with prostate cancer volume, was the first IGFBP protease biochemically identified.^{125,126} The current list falls into three major categories: kallikrein-like serine proteases, matrix metalloproteinases, and cathepsins⁶⁸. IGFBP proteolysis can be enhanced through increased protease expression by cancers or through protease activation by the tumor's acidic microenvironment^{68,127}.

Interestingly, IGFBP proteolysis also occurs at both the local and endocrine levels. Although the PSA elevation in prostate cancer patients' serum negatively correlates with the circulating level of intact IGFBP-3 (and positively with circulating IGFBP-2 levels)¹²⁸, the pattern of IGFBP-3 cleavage fragments in serum differs from that created by seminal PSA, so additional protease(s) must be involved⁶⁸. The frequency of supranormal plasma IGFBP-3 proteolysis was also found to increase with increasing stage of primary breast cancers¹²⁹.

4. Indirect Contributions

Cancer is a multigenetic phenomenon, and changes in the GH/IGF axis must be considered within the larger context of cellular signaling. Primary changes in the GH/IGF axis may impact the activities of other signaling pathways, and conversely, primary changes in other pathways may modify GH/IGF axis function.

4.1 GH

Although the somatomedin hypothesis identified IGF-I as the principal signaling target of GH, GH has been found to induce other downstream signaling molecules as well. These include: hepatocyte growth factor in the liver¹³⁰, epidermal growth factor (EGF) in the kidney¹³¹, basic fibroblast growth factor in chondrocytes¹³², interleukin-6 in osteoblasts¹³³, bone morphogenetic proteins 2 and 4 in fibroblasts¹³⁴, interleukin-1 α and β in the thymus¹³⁵, and preadipocyte factor-1 in beta cells¹³⁶. Whether GH contributes to the neoplastic process through downstream signaling molecules outside the IGF axis is yet unknown. In addition, GH was shown to induce phosphorylation of the EGF receptor (EGFR)¹³⁷; because phosphorylation slowed the rate of EGF-induced EGFR intracellular redistribution and degradation, GH cotreatment potentiated EGF-induced EGFR signaling¹³⁸. EGFR over-expression is one of the most common genetic lesions found in esophageal cancer¹³⁹, and IGFBP-3 induction was recently identified as a consequence of this over-expression¹⁴⁰. Cross-talk between the GH/IGF axis and EGF/EGFR pathways in the pathogenesis of esophageal cancer remains to be elucidated.

4.2 IGF-IGF-1R Signaling

IGF/IGF-1R signaling may contribute to cancer through interactions with oncogenes and other mitogens. For example, although IGF-1R was insufficient for growth in soft agar, it was required for malignant transformation by the SV40 large T antigen; stable transfection with SV40 large T antigen led to colony formation by *IGF-1R*^{+/+} but not *IGF-1R*^{-/-} cells¹⁴¹. Signal cooperation has also been shown between IGF-I and hepatocyte growth factor-scatter factor (HGF-SF) in hepatocellular carcinoma¹⁴² and granulocyte-monocyte-colony-stimulating factor (GM-CSF) in acute myeloid leukemic cells¹⁴³. Likewise, the IGF axis can interact with sex steroid systems to affect cancer development and behavior. This has been studied most for estrogen in breast cancer and androgens in prostate cancer. The interactions are bi-directional and frequently stage specific. Estrogen and IGF-I were synergistic in stimulating MCF-7 breast cancer cell proliferation; the combination enhanced G₁ phase progression through complementary regulation of p21, cyclin D1-CDK4 and cyclin E-CDK2 complexes^{144,145}. IGF1R overexpression has contributed to continued growth of estrogen-

deprived breast cancer cells¹⁴⁶ and androgen-independent prostate cancer cells¹⁴⁷. However, IGF-1R expression is lost as prostate cancers progress to metastases, an effect likely mediated by WT-1 (Wilm's tumor gene product)¹⁴⁸. One of the proposed mechanisms by which tamoxifen is beneficial for breast cancer treatment, beyond its estrogen inhibitory activity, is its reduction of serum IGF-I concentrations^{149,50}.

Many tumor suppressors, on the other hand, function at least in part by inhibiting IGF action. This may occur at the transcriptional or functional levels. Transcription of IGF-1R is repressed by WT-1¹⁵¹ and the tumor suppressor p53¹⁵². p53 also represses transcription of IGF-II¹⁵³, but stimulates transcription of IGFBP-3¹⁵⁴ (see Section 4.3). Other tumor suppressors can inhibit IGF action at the signaling level, without affecting transcription levels. PTEN (phosphatase and tensin homolog) is a phosphatase that dephosphorylates Akt, thereby inhibiting one of IGF's major signaling pathways^{155, 156}. Germline *PTEN* mutations have been detected in Cowden syndrome, characterized by multiorgan hamartomas and increased cancer risk, and allelic losses and somatic mutations at the *PTEN* locus are frequently found in cancers, especially in later stages as they become more aggressive^{157, 158}. The von Hippel Lindau gene product (VHL) leads to reduced VEGF production via ubiquitin-mediated degradation of HIF-1 α ¹⁵⁹. VHL was shown to also directly interact with protein kinase C- δ , causing its dissociation from IGF-1R and inhibition of IGF-mediated invasiveness¹⁶⁰. VHL is important in the pathogenesis of renal cell carcinoma, and its germline mutation causes a dominantly inherited familial cancer syndrome¹⁶¹.

4.3 IGFBP-3

As mentioned in the previous section, IGFBP-3 is transcriptionally induced by the tumor suppressor p53¹⁵⁴. In fact, IGFBP-3 was shown to mediate p53-induced apoptosis during serum starvation¹⁶², and multiple *p53* mutants that lost the ability to induce IGFBP-3 and Bax, but not p21, were unable to induce apoptosis^{163,164}. IGFBP-3 is also induced by cytokines, retinoic acid, DNA damage (both irradiation and drug-induced), and hypoxia^{110,165}. By inducing IGFBP-3 and repressing both IGF-1R/IGF-II, p53 switches the IGF axis balance from growth stimulation to growth inhibition and apoptosis. p53 is the most frequently mutated gene among all human cancers, and its germline mutation is associated with Li-Fraumeni Syndrome, another dominant familial cancer syndrome¹¹⁰.

Conversely, oncogenes can affect the IGF axis by inhibiting IGFBP-3 function. For example, oncogenic *H-ras* caused resistance to the growth-inhibitory effects of IGFBP-3 in breast cancer cells¹⁶⁶. E7, a product of human papillomaviruses associated with cervical cancer, was shown to bind IGFBP-3, leading to IGFBP-3 proteolysis and inhibition of IGFBP-3-induced apoptosis¹⁶⁷.

5. Clinical Implications

5.1 rhGH Treatment

Clinical practice with growth-promoting therapies has already been affected by the concern of possible cancer-promoting effects of GH and IGF-I. GH deficiency frequently develops as a consequence of irradiation or chemotherapy, and for intracranial neoplasms, from the

brain tumor itself or from tumor resection¹⁶⁸. Because the greatest risk of cancer recurrence is in the first year after treatment, current practice in many centers is to defer rhGH therapy until the patient is at least one year tumor-free. Yet when carefully studied, the evidence indicated that rhGH did not increase recurrence rates¹⁶⁹.

rhGH is currently accepted as a safe therapy, but there are two important considerations as we look to the future. First, rhGH therapy is evolving from limited physiologic replacement to increasingly pharmacologic use, in terms of escalating doses and additional indications¹⁷⁰. Its safety profile must be reevaluated in this new context. To guide continued safety, IGF-I levels in all rhGH recipients should be closely monitored and rhGH dose titrated to avoid supraphysiologic IGF-I levels.

Second, the follow-up study of the United Kingdom cadaveric pituitary GH recipients bears mentioning⁶. The significance of the results for current rhGH recipients is unclear. It is difficult to generalize from a sample size of two cases, and change in product makes comparisons dubious. Dosing schedule for rhGH is different than that for pituitary GH, and infectious risks have been eliminated by the switch to recombinant technology¹⁷¹. Just as Creutzfeldt-Jakob disease painfully exposed the incomplete purity of the pituitary GH, perhaps viral oncogenes were also transmitted? Yet the study pointed out a very important concept: because cancer incidence is greatest in older ages, ongoing surveillance of rhGH recipients into late adulthood is needed to fully assess the long-term safety.

5.2 Cancer Prevention

The ultimate goal of understanding how the GH/IGF axis may contribute to cancer is to devise ways of manipulating the system to prevent or treat cancer. Calorie restriction has long been recognized as an effective means of reducing circulating IGF-I levels. In cancer-susceptible mouse models, calorie restriction has been shown to not only lower IGF-I levels, but also to delay spontaneous tumor development and suppress carcinogen-induced tumor progression^{172,173}. For example, calorie restriction of p53-haploinsufficient mice suppressed progression of p-cresidine induced bladder tumors, but not when the circulating IGF-I levels were restored by pump infusion¹⁷⁴. In human epidemiologic studies, overweight has been the most reproducible cancer risk factor, so now the focus has shifted onto more prevention-oriented studies; physical exercise has been shown protective for breast and colon cancers¹⁷⁵, and several studies are trying to dissect out specific dietary components as particularly risk-affecting¹⁷⁶⁻¹⁷⁸. The burgeoning obesity epidemic throws urgency and keen interest upon this area of investigation, and opens up a new line of query as well: since the insulin-IR system is so closely related to the IGF axis and hyperinsulinemia is a frequent complication of obesity, the possible contributions of insulin to cancer remain to be explored.

5.3 Cancer Treatment

Forays into GH/IGF axis modulation as a means of treating cancer have fallen into two general categories: dampening the whole GH axis and more specifically targeting IGF/IGF-1R signaling. Table 4 summarizes the data from experiments using upstream targets¹⁷⁹⁻¹⁸⁴. To date, approaches for specifically inhibiting IGF-1R signaling include adenoviral

dominant negative IGF-1R¹⁸⁵, IGF-1R antibodies¹⁸⁶, IGF-1R antisense¹⁸⁷, IGF-1R siRNAs¹⁸⁸, and IGF-I antisense¹⁸⁹. The clinical efficacy of IGF-1R inhibition is yet unknown, as are the potential toxicities from inhibiting normal IGF-1R or cross-reactivity with IR. Thus this construes a hot area for on-going research.

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Figure 1.
Activation of Akt by IGF/IGF-1R signaling stimulates cell survival. (Modified from ref. 76).

Figure 2.
IGF-1R and Akt inactivation lead to apoptosis. (Modified from ref. 76.)

Table 1

Summary of data examining the association between T-to-A polymorphism and risk of colorectal neoplasia in Hawaiian populations. Based on data from ref. 24.

	T/T	T/A	A/A	P (trend)
IGF-I (ng/ml)	172.3	175.0	152.3	0.05
IGFBP-3 (ng/ml)	2859	3070	2792	0.05
Height (cm)	170.0	169.5	170.0	0.78
Overall				
OR colorectal cancer	1.00	0.75 [0.58–0.99]	0.62 [0.43–0.90]	0.006
OR adenoma	1.00	0.76 [0.46–1.24]	0.62 [0.31–1.22]	0.17
OR colorectal cancer				
Caucasian	1.0	0.85 [0.50–1.43]	0.44 [0.21–0.93]	0.05
Native Hawaiian	1.0	0.39 [0.16–0.94]	0.20 [0.07–0.59]	0.003
Japanese	1.0	0.79 [0.56–1.12]	0.85 [0.53–1.36]	0.34

OR = adjusted odds ratio; [] = 95% confidence intervals.

Table 2

Summary of studies associating cancer risk with circulating levels of IGF and IGFBPs.

Cancer	IGF axis component	Study design	Results	Ref.
Prostate				
	IGF-I IGFBP-3	Case (152)-control (152)	RR for highest quartile: IGF-I = 4.3 [1.8-10.6] IGFBP-3 = 0.41 [0.17-1.0]	28
	IGF-I IGFBP-3	Case (210)-control (224)	OR per 100 ng/ml increment of IGF-I: 1.51 [1.0-2.26] overall and 2.93 [1.43-5.97] for age less than 70 yrs No association with serum [IGFBP-3]	29
	IGF-I IGFBP-3	Case (149)-control (298)	Increased risk with increasing [IGF-I] ($p = 0.02$) and increasing [IGFBP-3] ($p = 0.03$) overall; for men age <59 yrs, association stronger for high [IGF-I] ($p = 0.01$), but [IGFBP-3] lost ($p = 0.44$)	30
	IGF-I	Meta-analysis	OR for highest quartile IGF-I similar to that for highest quartile of testosterone	31
	IGF-I IGFBP-3	Meta-analysis	OR for high IGF-I: 1.47 [1.23-1.77] OR for high IGFBP-3: 1.26 [1.03-1.54]	32
	IGF-I IGFBP-3	Case (530)-control (534)	For advanced-stage prostate cancer: RR for highest quartile IGF-I = 5.1 [2.0-13.2], high [BP-3] = 0.2 [0.1-0.6]. RR for combination high IGF-I/low BP-3 = 9.5 [1.9-48.4] Neither was predictive of early-stage cancer, nor associated with Gleason score.	33
	IGFBP-3 IGFBP-2	Pre-op in 120 men with localized disease (post-op in 51 of them) vs. 44 healthy men vs. 19 nodal mets vs. 10 bone mets	[IGFBP-3] lowest in men with bone mets. [IGFBP-2] higher in cancer patients than healthy men and declined with prostatectomy. Among cancer patients, [IGFBP-2] was lower with advanced disease and larger tumor volume.	34
Gastrointestinal				
Colorectal cancer	IGF-I IGFBP-3 IGF-II	case (193)-control (318) men only	RR for highest quintile IGF-I = 2.51 [1.15-5.46] IGFBP-3 = 0.28 [0.012-0.66] IGF-II not associated with risk.	35
	IGFBP-1,2,3	case (102)-control (200) women only	OR for highest quintile IGFBP-1 = 0.48[0.23-1.0] IGFBP-2 = 0.38[0.015-0.094] IGFBP-3 = 2.46[1.09-5.57]	36
	IGF-II IGFBP-2	case (92)-control (57)	IGF-II elevated in Dukes A and B, but not advanced disease. IGFBP-2 related to tumor burden and fell with curative resection	37
Colorectal adenoma	IGF-II	case (52)-control (293)	OR for adenoma per SD change: IGF-II = 3.05[2.04-4.57] IGFBP-2 = 2.26[1.53-3.44]	38
Gastric adenocarcinoma	IGF-I IGFBP-3	26 cases pre-op and post-op days 14 and 50.	All 26 had IGF-I over the normal limits pre-op that significantly decreased post-op but not to normal. IGFBP-3 also high pre-op.	39
Lung				
	IGF-I IGFBP-3 IGF-II	case (204)-control (218)	OR for highest quartile IGF-I = 2.06[1.19-3.56] IGFBP-3 = 0.48[0.25-0.92] IGF-II not associated with risk.	40
	IGF-I IGFBP-1,2,3	case (93)-control (186) Women only	No associations found.	41

Cancer	IGF axis component	Study design	Results	Ref.
GYN Breast cancer	IGF-I IGFBP-3	case (230)–control (659) Men only	IGF-I not associated. OR highest quartile of IGFBP-3: All cases: 0.50[0.25-1.02] Ever smokers (n = 184): 0.41[0.018-0.92]	42
	IGF-I	case (397) –control (620)	Post-menopausal: no association. Premenopausal: RR for top tertile All = 2.33 [1.06-5.16] Age < 50 yrs = 4.58[1.75-12.0] Adjusting for IGFBP-3 raised the RR's All = 2.88[1.21-6.85] Age < 50 yrs = 7.28[2.40-22.0]	43
	IGF-I IGFBP-1,3	case (63)–control (27)	IGF-I levels similar, OR for high: IGFBP-3 = 0.18[0.05-0.55] IGFBP-1 = 0.21 [0.07-0.68]	44
	IGF-I IGFBP-3	case (40)–control (40)	OR for high free IGF-I = 6.31 [1.03-38.72]. High total IGF-I/intact IGFBP-3 ratio, OR = 3.35[1.08-10.36]	45
	IGF-I IGFBP-1,2,3	case (149)–control (333) only postmenopausal.	No associations found.	46
Ovarian cancer	Number of CA repeats In IGF-I gene	Case (53)–control (53)	19 repeats: OR = 2.87[1.16-7.06] Both 19 repeats and high plasma IGF-I: OR = 5.12[1.42-18.5]	47
	IGF-I	Case (132)–control (263)	All: no association. Age < 55yrs: top tertile OR = 4.97[1.22-20.2]	48
	IGF-I IGF-II	Case (84)–control (84)	IGF-I: inverse association IGF-II: positive association	49
Bladder cancer	IGF-I IGFBP-3	Case (154)–control (154)	OR for highest quartile IGF-I = 3.10[1.43-6.70] IGFBP-3 = 0.38[0.19-0.78] IGF-I/IGFBP-3 molar ratio = 4.30[1.99-9.28]	50

* numbers in parentheses refer to sample sizes for the case-control studies. [] = 95% confidence intervals for odds ratios and relative risks.

Table 3

Summary of IGF and insulin receptors.

Receptor	Structure	Ligands*	Characteristics	Function
IGF-IR	Transmembrane $\alpha_2\beta_2$ tyrosine kinase	IGF-I IGF-II	Ubiquitous; important for normal growth	cell survival, mitogenesis, transformation
IGF-2R	Identical to mannose-6-phosphate receptor	IGF-II	Soluble receptor	clear IGF-II from the circulation
IRA	Transmembrane $\alpha_2\beta_2$ tyrosine kinase	IGF-II insulin	Predominant IR isoform in fetal tissues; shorter (12 amino acids omitted from α -subunit by skipping exon 11)	fetal growth, metabolism
IR-B	Transmembrane $\alpha_2\beta_2$ tyrosine kinase	insulin	Longer IR isoform; found in metabolically responsive adult tissues (fat, liver, muscle)	glucose storage and oxidation, lipid storage, protein synthesis, regulation of gene expression cell survival, mitogenesis, transformation
Hybrids	Transmembrane $\alpha_2\beta_2$ tyrosine kinase	IGF-I	Random assembly of an IR hemireceptor combined with an IGF-1R hemireceptor	

* Ligands listed refer to high-affinity binding only.

Table 4

GH antagonism to reduce IGF-I and inhibit cancer. Antag, antagonist; cx, tissue culture; deer, decrease; incr, increase; prolif, proliferation.

GH antagonist	Model system	Effect	Ref.
GH-R antag (pegvisomant)	Meningiomas xenografted into athymic mice; animals treated X 8wks	Deer tumor volume and tumor weight. Serum [IGF-1] and [BP-3] deer; [BP-1] and [BP-4]incr. No difference in tumor [IGF-I]	179
-+ Transgenic mice with GH-antag	DMB A-induced mammary tumors	Transgenic mice smaller, deer [IGF-I]. Deer tumor incidence.	180
GH-RH antag (MZ-4-71)	Caki-I (renal adenoCA) Tissue ex and xenografted into nude mice	Mice: deer tumor volume; deer tumor weight. Deer serum [GH] and [IGF-I]. Also deer [IGF-I] in liver and tumor; deer [IGF-II] in tumor. Cx: inhibit growth, but only at high concentrations.	181
GH-RH antags (MZ-4-71, MZ5-156 and JV-1-36)	HT-29 (colon CA): Tissue ex and xenografted into nude mice	Mice: deer tumor volume and weight by all 3 agents. Deer cell prolif, incr apoptosis; deer tumor IGF-II. No change in serum [IGF-I] or [IGF-II]. Cx: MZ-5-156 dose-dependently deer IGF-II and cell prolif.	182
GH-RH antag (JV-1-38); somatostatin analog (RC-160)	PC-3 (prostate CA): Tissue ex and xenografted into nude mice	Mice: tumor volume deer 49% by JV-1-38, 30% (NS) by RC-160, 63% by combination. Deer serum [IGF-I] by RC-160 only; deer tumor IGF-II mRNA by both; deer VEGF by both. Cx: cell prolif inhibited by JV-1-38, not RC-160 alone but moreso in combination.	183
GH-RH antag (JV-1-38)	MNNG/HOS (osteosarcoma) and SK-ES-1 (Ewing's sarcoma): Tissue ex and xenografted into nude mice	Mice: tumor volume and weight deer for both, incr tumor doubling time. Deer [IGF-I] in serum and liver mRNA; Deer [IGF-II] and IGF-II mRNA in both tumors. Cx: inhibited prolif of both cell lines.	184