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Mini-review

The insulin-like growth factor system and cancer

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Abstract

The insulin-like growth factor (IGF) family of ligands, binding proteins and receptors is an important growth factor system involved in both the development of the organism and the maintenance of normal function of many cells of the body. The system also has powerful anti-apoptotic effects. More recently, evidence has accrued to demonstrate that the IGFs play an important role in cancer. Individuals with serum IGF-II levels in the upper quartile of the normal range (and IGF binding protein-3 levels in the lower quartiles) have a relative risk for developing breast, prostate, colon and lung cancer. IGF-II is commonly expressed by tumor cells and may act as an autocrine growth factor; occasionally even reaching target tissues and causing tumor-induced hypoglycemia. The IGF-I receptor is commonly (though not always) overexpressed in many cancers, and many recent studies have identified new signaling pathways emanating from the IGF-I receptor that affect cancer cell proliferation, adhesion, migration and cell death; functions that are critical for cancer cell survival and metastases. In this review, many aspects of the IGF system and its relationship to cancer will be discussed.
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Keywords: Insulin-like growth factor; Insulin receptor; Cancer

1. Introduction

The insulin-like growth factor (IGF) signaling system plays a critical role in the growth and development of many tissues and regulates overall growth, particularly prenatal growth. The IGF system has also been implicated in various pathophysiological conditions, and is thought to play a particularly prominent role in tumorigenesis. The IGF system is comprised of the IGF ligands (IGF-I and IGF-II), cell-surface receptors that mediate the biological effects of the IGFs, including the IGF-I receptor (IGF-IR), the IGF-II receptor (IGF-IIR), and the insulin receptor (IR), as well as a family of IGF-binding proteins (IGFBPs). IGFBPs affect the half-lives and bioavailability of the IGFs in the circulation, in extracellular fluids, and may exert IGF-independent effects under certain conditions (Fig. 1). This review will focus on the structure and function of the three components of the IGF axis, their interactions, and their role in tumorigenesis. For reviews on the IGF system see Refs. [1–3].

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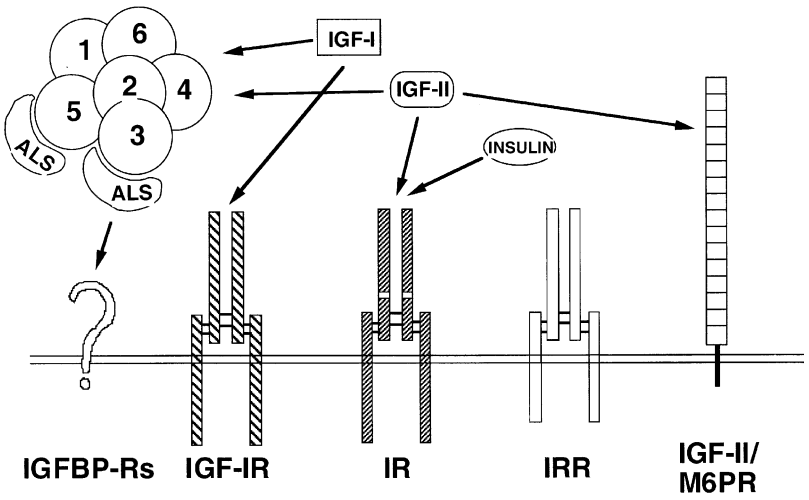

Fig. 1. The IGF system. Shown are the ligands, cell-surface receptors, and the IGF-binding proteins that constitute the IGF system. As indicated, IGF-I interacts with the IGF-IR and the IGFBPs, IGF-II interacts with the IGF-IR, the IGF-IIR, the exon 11-lacking (A) form of the IR, and the IGFBPs, and insulin interacts with the IR. Some of the IGFBPs exert effects that are independent of their modulation of IGF signaling through the IGF-IR and the IR, and these may involve novel IGFBP receptors.

2. The IGF ligands

2.1. Structure of IGF-I and IGF-II

The mature IGF-I and IGF-II peptides consist of B and A domains that are homologous to the B and A chains of insulin. Unlike insulin, the IGF peptides are not prototypically cleaved, but remain linked in the mature peptides by C domains analogous to the C peptide of insulin. Both IGF-I and IGF-II contain an additional short D domain that is not found in insulin. The IGF-I and IGF-II prohormones contain a C-terminal E peptide that is cleaved in the Golgi apparatus during secretion [4].

2.2. Expression of IGF-I and IGF-II

The prenatal expression of the IGF-II gene is widespread in rodents and diminishes dramatically after birth, with only the choroid plexus and the leptomeninges persistently synthesizing IGF-II in adult animals. In contrast, murine expression of IGF-I is low during the prenatal period and increases significantly during puberty and adulthood, when hepatic production becomes a major contributor to overall circulating IGF-I levels. IGF-I exerts endocrine, paracrine, and autocrine effects, and is produced by numerous other adult organs, including kidney, lung, and bone. The overall picture of IGF expression in rodents initially led to the concept of IGF-II as a fetal growth factor and IGF-I as an adult growth factor. However, this expression pattern is not observed in humans, as both IGF-I and IGF-II are produced in multiple human tissues throughout life. In fact, the circulating levels of human IGF-II are consistently several-fold higher than that of IGF-I, which is consistent with the concept that IGF-I and IGF-II have potentially divergent roles in human physiology [4].

3. The IGF receptors

3.1. IGF and insulin receptors

The IGF-I and IGF-II ligands interact with an array of cell-surface receptors that may be present singly or in various combinations on target cells. Both IGF-I and IGF-II interact with the IGF-IR, a trans-membrane tyrosine kinase that is structurally and functionally related to the IR. IGF-II can also bind to the IGF-IIR with high affinity. Cloning of the IGF-IIR cDNA revealed that it is identical to the previously characterized cation-independent

mannose-6-phosphate (M6P) receptor, which plays a role in endocytosis and intracellular trafficking of M6P-tagged proteins. This molecule is thought to function as a clearance receptor for IGF-II, thereby influencing the extracellular levels of IGF-II [3].

Most, if not all, of the effects of IGF-I result from its activation of the IGF-IR. IGF-I does not cross-react with the IR, except at pharmacological doses, since IGF-I has a relative affinity almost two orders of magnitude higher for the IGF-IR, as compared to the IR. Until recently, it was thought that IGF-II, like IGF-I, bound at significant levels to the IGF-IR, but not the IR. Studies of knockout mice lacking various components of the IGF and insulin receptor systems suggested that IGF-II acted through the IR during the early stages of development, before IGF-IR gene expression was detectable [5]. The molecular basis for this phenomenon was revealed when it was discovered that a splice variant of the IR displayed high affinity for IGF-II. The IR transcript is subject to alternative splicing of exon 11, which encodes a 12-amino acid segment in the C-terminus of the extracellular subunit. Previous studies had shown that the IR isoform encoded by the mRNA lacking the exon 11 sequence (IR-A) displayed a 2-fold higher affinity for insulin than the IR-B isoform, which includes exon 11. More recently, it has been reported that the IR-A isoform functions as a high-affinity receptor for IGF-II and mediates predominantly proliferative effects, as compared to the principally metabolic effects elicited by insulin stimulation of the IR-B isoform [6]. Thus, IGF-I functions primarily by activating the IGF-IR, whereas IGF-II can act through either the IGF-IR or through the IR-A isoform.

3.2. Hybrid receptors

The complexity of IGF signaling is increased by the formation of hybrid receptors that result from the dimerization of IGF-IR and IR hemireceptors. Each hybrid receptor consists of a single α and β subunit linked by disulfide bonds, which are formed in the Golgi apparatus of cells expressing both the IGF-IR and the IR. This could be due to the preferential formation of disulfide bonds between cysteine residues in IGF-IR and IR subunits themselves. Thus, in some circumstances, hybrid receptors may outnumber homoreceptor molecules at the cell surface.

IGF-IR/IR hybrid receptors retain high affinity for IGF-I, but exhibit a dramatically decreased affinity for insulin. This is thought to reflect the ability of IGF-I to efficiently bind to either IGF-IR α subunit, whereas tight insulin binding requires interaction with both of the β subunits found in the IR. Thus, the presence of a significant number of hybrid receptors may selectively diminish cellular responsiveness to insulin, but not to IGF-I. Indeed, this has been proposed as a mechanism by which up-regulation of IGF-IR expression could cause insulin resistance in cells that express the IR. The effects of hybrid receptors are further complicated by the presence of the IR-A and IR-B isoforms and their different IGF-II-binding characteristics. It is likely that hybrids form between both IR-A/IGF-IR and IR-B/IGF-IR form, since most cell express both splice variants. It has been recently demonstrated that IGF-IR/IR-A hybrids bind IGF-I, IGF-II, and insulin, whereas IGF-IR/IR-B hybrids bind IGF-I with high affinity, IGF-II with low affinity, and do not bind insulin [7]. Therefore, the relative expression of the IGF-IR and IR genes and the degree of alternative splicing of exon 11 of the IR gene governs the ability of a given cell to respond to IGF-I, IGF-II, and insulin. Confirmed and potential receptor hybrids that may be involved in IGF signaling are shown in Fig. 2.

3.3. IGF-IR and IR signal transduction

The various signaling pathways regulated by the IGFs are largely represented by those identified to date for the IGF-IR (Fig. 3). When IGF-I or IGF-II binds to the extracellular subunit of the IGF-IR, a conformational change is induced in the transmembrane β subunits, resulting in trans-autophosphorylation of the cytoplasmic tyrosine kinase domain of the β subunit. This fully activates the receptor tyrosine kinase, which then autophosphorylates additional tyrosine residues in the juxtamembrane and carboxyl-terminal domains flanking the tyrosine kinase domain. These phosphorylated residues, particularly tyrosine 950 in the juxtamembrane domain, can then function as docking sites for the insulin receptor substrate (IRS) and Shc adaptor proteins. Tyrosine phosphorylation of these proteins by the receptor tyrosine kinase allows IRS and Shc proteins to recruit other factors, such as Grb2/SOS and

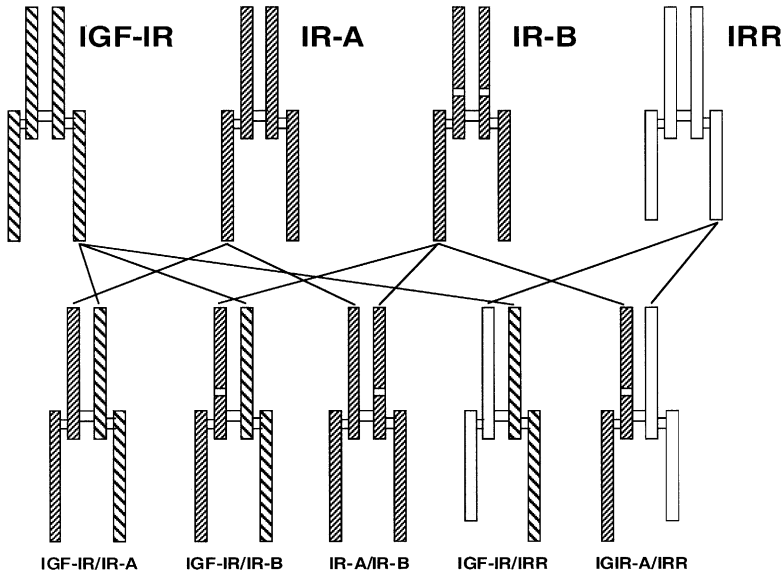

Fig. 2. Hybrid receptors involved in IGF signaling. Shown are hybrids involving the IGF-IR, IR-A, IR-B, and the IRR that are involved in IGF signaling. IGF-IR/IRR hybrids have not been demonstrated to date, but their existence is inferred from the ability of the IR and the IRR to form hybrids in engineered cells. IR-B/IRR hybrids are also a formal possibility, but would not be expected to be involved in IGF signaling, since they would presumably not bind IGFs or insulin.

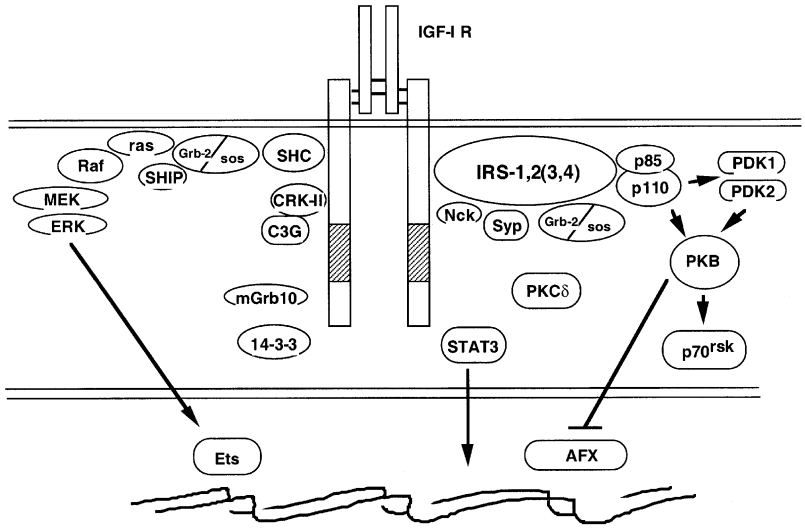

Fig. 3. IGF-IR signal transduction cascades. The activated IGF-IR initiates signaling through two primary cascades, the MAP kinase and PI3 kinase pathways. As shown, IRS proteins couple the receptor to the PI3 kinase cascade, while Shc couples the receptor to the MAP kinase cascade. In addition, IRS proteins, through their association with Grb-2/SOS, also couple to the MAP kinase pathway, while Shc, through interaction with the IRS homologs Gab-1 or Gab-2, can activate the PI3 kinase pathway. Thus, IRS proteins and Shc both integrate IGF activation of these two signaling pathways. A number of other factors, some of which are illustrated, have been shown to interact with or be in some way involved in IGF-IR action.

the p85 regulatory subunit of phosphatidyl inositol 3′-kinase (PI3 kinase), thereby leading to activation of the mitogen-activated protein kinase (MAP kinase) and PI3 kinase cascades, which are the major signal transduction cascades triggered by the activated IGF-IR. The ultimate targets of the MAP kinase and PI3 kinase cascades include members of the Ets and forkhead transcription factor families. Regulation of transcription factors provides a mechanism by which IGF action at the cell surface can elicit changes in gene expression that eventually mediate the proliferative, differentiative, and apoptotic effects of IGFs [3].

While IGF action can clearly be controlled by the levels of extracellular ligands and the particular combination of receptors at the cell surface, the relative abundance of downstream receptor targets may also be an important factor in determining the effects of IGFs in a given target cell. The IRS proteins are early substrates of the IGF-IR and IR, and function as docking proteins that link these receptors to various downstream signaling pathways. The four members of the IRS family of proteins, IRS-1 through 4, share a high degree of similarity, yet each has a unique structure [8]. The presence of different combinations of IRS proteins may result in different cellular responses to activation of the IGF-IR. In fact, recent studies have suggested that IRS-3 and IRS-4 can actually *inhibit* processes that are mediated through IRS-1 and IRS-2. The relative levels of Shc and IRS proteins may also be important for influencing IGF action, in that Shc and IRS proteins have been shown to compete for binding to tyrosine 950 of the activated IGF-IR.

4. IGFBP

The biological activities of the IGF ligands are also modulated by a family of high-affinity IGFBP-1 through 6 that are found in the circulation and in extracellular fluids. IGFBP-3 is the predominant IGFBP in serum, and most circulating IGF-I and IGF-II is not found in a free form, but in a ternary complex with IGFBP-3 and a third component, the acid-labile subunit (ALS), in a 1:1:1 molar ratio. IGFBP-5 also forms ternary complexes with IGFs and ALS. While IGFBPs-1 through 4 generally have similar affinities for IGF-I and IGF-II, IGFBP-5 and 6 bind IGF-II with 10- and 100-fold greater affinities, respectively, than IGF-I. The IGFBPs do not bind insulin. The IGFBPs control IGF action by increasing the half-lives of circulating IGFs, by controlling their availability for receptor binding, and, in the case of cell surface-associated IGFBPs, by potentially influencing their direct interaction with receptors. Each of the IGFBPs is subject to limited, and potentially regulated, proteolysis by various proteases. Thus, ligand-receptor interactions in the IGF system are subject to complex regulation as a result of the levels of IGFBPs, their expression profile, the degree of cell-surface association, and the extent of proteolysis [1].

A series of studies performed over the past several years has established that certain actions of the IGFBPs are IGF-independent. IGFPB-3 and IGFBP-5, in particular, have been shown to exhibit effects on proliferation, migration, and sensitivity to apoptosis that are independent of their effects on IGF signaling per se. Some of these IGF-independent effects are still modulated by IGF binding to the particular IGFBP, so ‘IGF receptor-independent actions’ may be a more accurate term for these novel functions. The cell surface and/or intracellular molecules that participate in these effects have not been well-characterized, but exposure to exogenous recombinant IGFBP-3 and IGFBP-5 proteins has been shown to induce nuclear localization of these proteins. A better characterization of the IGF receptor-independent actions of IGFBPs will provide an important new dimension to our understanding of the IGF signaling system in general.

5. Physiological and pathophysiological aspects of IGF action

The IGF system plays an important role in normal growth and development as well as in a variety of pathological situations, particularly tumorigenesis [9]. IGF action is also important in the development of specific organs, such as in the nervous system, in which IGF signaling regulates neuronal proliferation, apoptosis, and cell survival.

IGF action plays a critical role in the development and progression of human cancer. A growing body of epidemiological data suggests that high levels of

circulating IGF-I constitute a risk factor for the development of breast, prostate, colon, and lung cancer. In addition, the expression levels of the IGF-IR and IR are predictive of breast cancer outcome. Experimentally, modulation of IGF-IR activity affects the growth of many types of tumor cells. As a result of these findings, intensive effort is being directed towards investigating the utility of the IGF system as both a diagnostic marker and a therapeutic target in cancer therapy, as outlined in more detail below.

5.1. Role of IGF-IR signaling cascade in cancer cell function

Regulation of IGF-IR gene expression is closely associated with the function of a variety of tumor suppressor genes and oncogenes. The p53 tumor suppressor protein protects mammalian cells against cancer. A large number of human cancers exhibit mutations within the p53 gene that either impair its tumor suppressor function or provide it with oncogenic potential. Expression of wild-type p53 inhibits IGF-IR gene expression, whereas mutant p53 upregulates IGF-IR gene expression [10]. Mdm-2 targets p53 for degradation; an Mdm-2-mediated reduction in p53 could thereby induce upregulation of the IGF-IR and increase the survival of cancer cells [11]. Expression of the IGF-IR is also regulated by the Src tyrosine kinase, the PKB/Akt serine-threonine kinase, and the PTEN protein phosphatase. Constitutively active Akt or Src-activated Akt upregulates IGF-IR gene expression, whereas PTEN counteracts this effect in pancreatic cancer cells and renders the cells more invasive [12].

Neuronuclear factor (NF)-κB is a transcription factor that can function in both cytokine signaling and in cell survival. NF-κB mediates anti-apoptotic effects of IGF-I in colon cancer cells [13], whereas it can mediate pro-apoptotic effects under other circumstances, such as its role in the effects of tumor necrosis factor-α [14]. Thus, the specific cellular response to NF-κB depends on the original stimulus.

Migration of epithelial colonic cells is dependent on IGF-IR-induced alterations in integrins and cell adhesion complexes. While IGF-IR activation did not alter integrin expression levels, most of the integrins re-localized to the leading edge of migrating cells in response to IGF-I stimulation. Blocking integrin function with specific antibodies inhibited IGF-I-induced migration. Furthermore, activation of the IGF-IR disrupts the E-cadherin/catenin complex and its association with the cytoskeleton [15]. Similarly, in MCF-7 breast cancer cells, the IGF-IR was shown to directly interact with the cell adhesion complex comprised of E-cadherin, β-catenin, and p120 catenin. When IGF-IR antisense mRNA was expressed in MCF-7 cells, the cells exhibited a more malignant phenotype that was associated with a reduction in the cell–cell adhesion complex. This reduction was proposed to arise from a p120 catenin-induced decrease in E-cadherin and activation of Rac and Cdc42 activity [16].

Certain tumor cells exhibit growth factor dependence early during the progression of tumorigenesis. During later stages, such cells may become growth factor-independent for continued progression. For example, early-stage melanoma cells have recently been shown to be exquisitely sensitive to IGF-I. At these early stages, IGF-I activates the MAP kinase pathway, which triggers proliferation, and the PI3 kinase pathway, which promotes cell survival and stabilization of β-catenin. At later stages of development, i.e. in malignant melanoma cells, Erk1 and Erk2 were constitutively activated and β-catenin became more stabilized; IGF-I was unable to further activate these systems [17].

Cross-talk between receptors and their signaling pathways has been recently shown to play a critical role in various cellular responses to ligands. Such cross-talk may occur between receptors within the same family, such as the epidermal growth factor (EGF) and IGF-I receptors, which are both tyrosine kinase receptors [18] or between different families such as nuclear steroid receptors and the IGF-IR [19] or G protein-coupled receptors and the IGF-IR [20]. For example, the GBM(R) glioblastoma cell line is insensitive to AG1478, an anti-EGF therapeutic agent that acts as a specific EGF receptor tyrosine kinase inhibitor. GBM(R) cells exhibited compensatory upregulation of IGF-IR levels in response to AG1478 treatment. This resulted in persistent signaling through the PI3 kinase pathway and was associated with an anti-apoptotic and proinvasive phenotype. Both Akt1 and p70S6K appeared to play a role in this process [21]. In another example, the IGF-IR also protects mammary epithelial cells from apoptosis.

Activation of the IGF-IR induces serine phosphorylation of BAD in this cell type, but this is mediated via transactivation of the EGF receptor, as this effect was blocked by ZD1839, a specific EGFR tyrosine kinase antagonist [18].

Motility is an important process that plays a role in the spread of cancer cells. Activation of the IGF-IR and subsequent activation of the PI3 kinase and MAP kinase pathways induces extension of lamellipodia in neuroblastoma cell lines [22]. Migration of melanoma cells is also stimulated by IGF-I. This effect is mediated by upregulation of interleukin-8 gene expression via IGF-I-induced activation of MAP kinase and phosphorylation of c-Jun [23].

Various strategies have been used to block the IGF-IR in order to prevent tumor cell growth and to increase apoptosis of malignant cells. Expression of a dominant-negative truncated IGF-IR in colon cancer cells reduced the level of vascular endothelial growth factor expression, impaired tumor progression in nude mice, and increased tumor cell apoptosis [24]. Scotlandi et al. overexpressed a dominant-negative form of the IGF-IR with a mutated ATP-binding site in Ewing's sarcoma cells. This resulted in enhanced apoptosis, decreased tumorigenesis, and increased sensitivity to chemotherapeutic agents [25]. Other techniques that have been used to inactivate the IGF-IR include expression of truncated soluble receptors to prevent ligand-receptor interactions [26] and expression of peptides that could interfere with these interactions [27]. Perhaps the most exciting potential therapeutic modalities will arise from the recent crystallographic studies of the tyrosine kinase domain of the IGF-IR [28–30] and the production of small molecules that can act as specific antagonists for the IGF-IR and inhibit its anti-apoptotic effects [31].

5.2. Role of circulating IGF in specific human cancers

5.2.1. Prostate cancer

The potent mitogenic activity of IGF-I in cell culture made it an obvious candidate risk factor in cancer development, but it was not until 1998 that several prospective studies suggested that high circulating levels of IGF-I were associated with an increased risk of developing prostate cancer [32,33].

A significant amount of data had been accumulated that suggested that the IGF system plays an important role in the prostate. Prostatic stromal cells and epithelial cells in primary culture secrete IGFBPs and stromal cells produce IGF-II, and both stromal and epithelial cells express the IGF-I receptor and are responsive to IGF-I with respect to proliferation [34–36]. In vivo, it is likely that the prostate epithelial cells that are the precursors to prostatic intraepithelial neoplasia and prostatic adenocarcinoma respond to both locally produced IGF-II and circulating IGF-I through paracrine and endocrine mechanisms, respectively. Further support for the role of IGF action in prostate growth has come from recent reports that systemic administration of IGF-I increases rat prostate growth [37], that modulation of rat ventral prostate weight by finasteride is associated with altered levels of IGF-I receptors and IGFBP-3 gene expression [38], and that IGF-I-deficient mice exhibit decreased prostate size and complexity of prostate structure [39].

The validity of the association between IGF-I levels and prostate cancer risk was questioned by subsequent cross-sectional studies [40,41], in a prospective study, found that the IGF-I/PSA ratio was superior to IGF-I or PSA measurements alone for predicting prostate cancer risk

Finne et al. [42], in a screening trial, did not find an association between serum IGF-I levels and prostate cancer risk, while Baffa et al. [43] actually found that circulating IGF-I levels were lower in a group of patients undergoing radical prostatectomy as compared to age-matched controls. In prospective studies, however, Harman et al. [44] and Stattin et al. [45] found that IGF-I levels were associated with prostate cancer risk, and that this association was especially evident in younger men.

While the conclusions of this extensive series of studies conducted over the last 4 years appear contradictory, there is, in fact, some consistency. Prospective studies consistently demonstrate an association between high circulating IGF-I levels and prostate cancer risk, while cross-sectional studies have generated variable results. These data are consistent with the hypothesis that high serum IGF-I levels in younger men predict the occurrence of advanced prostate cancer years later, while IGF-I levels at the time of diagnosis are not especially informative. This hypothesis suggests that long-term exposure of prostate epithelial cells to high levels of

serum-derived IGF-I increases the probability of initiating hyperplasia in the cellular precursors of prostatic intraepithelial neoplasia and subsequent prostate adenocarcinoma.

Molecular corroboration of the relationship between IGF-I levels and prostate carcinogenesis has now come from analysis of transgenic mice with targeted expression of IGF-I in the basal prostatic epithelium. This dysregulated IGF-I biosynthesis resulted in the appearance of hyperplastic lesions resembling PIN by 6 months of age, and prostatic adenocarcinomas or small cell carcinomas were eventually seen in 50% of the transgenics. Specifically, deregulated expression of IGF-I and constitutive activation of IGF-I receptors in basal epithelial cells resulted in tumor progression similar to that seen in human disease. These studies also provide additional evidence for the prostate basal epithelial cell as a precursor to prostate cancer.

5.2.2. Breast and other cancers

In 1998, Hawkinson et al. [46] reported that premenopausal, but not post-menopausal women in the highest tertile of serum IGF-I levels had a significantly increased risk of developing breast cancer. These findings have been generally supported by most [47] but not all [48] subsequent studies. Racial factors may play a role in the IGF-I-breast cancer association, in that Agurs-Collins et al. [49] found that high serum IGF-I levels were strongly associated with breast cancer risk in postmenopausal African-American women.

With respect to colorectal cancer, Ma et al. [50] and Palmquist et al. [51] have reported positive associations between serum IGF-I and colorectal cancer risk in US, Greek and Swedish cohorts, while Probst-Hensch et al. [52] found an association between IGF-I or IGFBP-3 levels and colorectal cancer risk in a Chinese cohort. The role of IGF-II is also unclear, being positively associated in the Greek and Chinese studies, but not in the US cohort.

Yu et al. [53] reported a positive association between high IGF-I and low IGFBP-3 levels (but not IGF-II) and lung cancer risk. Lukanova et al. [54], however, found no correlation between serum IGF-I or IGFBPs in a large female cohort.

Collectively, these studies continue to suggest a role for IGF-I as a risk factor for breast, colorectal, and lung cancer, but its utility as a pragmatic marker is potentially limited by ethnic and (for colorectal and lung cancer) gender factors.

5.3. The role of the IGF-IR in human cancer

Numerous studies performed over the last 20 years have suggested that transformed cells express the IGF-IR at higher levels than normal cells. However, the molecular mechanisms by which IGF-IR gene expression is increased in tumors remain largely unidentified. Amplification of the IGF-IR locus at band 15q26 has been reported in a small number of breast cancer and melanoma cases [55]. During tumorigenesis, overexpression of the IGF-IR is presumed to increase the cellular responsiveness to the IGFs, in terms of proliferation and inhibition of apoptosis. This picture is probably most accurate with respect to the pediatric tumors associated with chromosomal translocations, such as Wilms' tumor and rhabdomyosarcoma. However, the role of the IGF-IR in the progression of epithelial tumors that are most prevalent in adults is likely to be more complex [56]. It has been suggested that the IGF-IR itself can function as an oncogene, based upon the phenotype of fibroblasts overexpressing the IGF-IR [57]. However, the relevance of this system to human cancer in general is unclear. Other studies have used IGF-IR overexpression in fibroblasts to show that the IGF-IR can modulate radiosensitivity [58]. Nevertheless, it should be noted that a recent report demonstrated that inhibition of IGF-IR activity by a selective kinase inhibitor in MCF-7 breast cancer cells increases radiosensitivity [59].

The many studies describing over-expression of the IGF-IR in breast, prostate, and other tumor types have been largely based on analyses of tissue homogenates or established cancer cell lines. Unfortunately, there are no appropriate normal controls for these samples that can be used for comparison. The apparent IGF-IR content of tissue homogenates, in particular, can be affected by contamination with stroma, which would dilute the IGF-IR content in normal epithelium or small tumors. More focused studies of IGF-IR expression in breast and prostate that employed immunohistochemistry or matched cell lines corresponding to normal and tumor tissue

revealed that normal epithelium and early-stage tumors both express abundant levels of the IGF-IR, and that IGF-IR expression is significantly reduced in advanced, metastatic cancer [60–64]. A recent report by Hellawell et al. [65] challenged this view, reporting that IGF-IR expression was decreased in certain metastatic prostate cancer samples, as compared to benign or carcinoma tissue, but that IGF-IR expression was increased in the majority of samples studied (eight out of 12). However, it should be noted that IGF-IR immunostaining with a single β-subunit antibody was diffusely cytoplasmic in most samples, in contrast to the expected membrane localization reported by Chott et al. [62], who used two different α-subunit antibodies. Thus, the levels of IGF-IR expression in the progression of prostate cancer have not been clearly established. Activation of the IGF-IR present in normal epithelium in response to elevated levels of circulating IGF-I may underlie the epidemiological data described above. In contrast, the subsequent decrease in IGF-IR (if this is substantiated by additional studies) may represent an attempt by established cancer cells to counteract the potential differentiating effects of IGF-I at sites of metastasis. Alternatively, decreased expression of the IGF-IR may protect tumor cells from a novel, non-apoptotic form of programmed cell death that has been recently described as being triggered by the unliganded IGF-IR [66]. It is clear, however, that the prevailing notion that the IGF-IR is routinely over-expressed in transformed cells is somewhat of an over-generalization.

6. Summary

In summary, the IGF signaling system plays a central role in many aspects of tumorigenesis. A better understanding of this complex system will facilitate the development of novel approaches to diagnose and treat various human cancers.

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