Insulin-like growth factors and prostate cancer

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Abstract

Converging data from epidemiological and biological research implicate insulin-like growth factor (IGF) physiology in the regulation of prostate epithelial cell proliferation and in the pathophysiology of prostate cancer. This review (1) outlines elements of IGF physiology, (2) reviews recent evidence that circulating IGF-I level is related to risk of prostate cancer, (3) provides a hypothesis concerning the biological basis for the relationship between IGF-1 level and risk of prostate cancer, (4) discusses IGF-I physiology in the context of neoplastic progression of prostate cancer, and (5) discusses clinical implications of these lines of research with respect to prevention and treatment.

Background

Unlike many other regulatory peptides, insulin-like growth factor I (IGF-I) has characteristics of both a tissue growth factor and an endocrine hormone [1]. Circulating IGF-I originates chiefly from the liver, and serum levels are subject to complex physiological regulation. For example, IGF-I gene expression is upregulated by growth hormone from the pituitary (which is itself subject to feedback inhibition by IGF-I, upregulation by growth hormone releasing hormone (GHRH) and downregulation by somatostatin) and downregulated by caloric restriction [2]. It must be emphasized that there is considerable inter-individual variation in IGF-I levels. The normal range has been difficult to define because of the extent of the variability, but one survey shows the mean ± two standard deviations in young men to be 350 ± 150 ng/ml [3]. Relative to other hormones, IGF-I levels for a given individual tend to be stable over time, although there is a gradual decline over decades post adolescence.

IGFs circulate complexed with specific high affinity IGF binding proteins (IGFBPs). More than half a dozen of these molecules have been characterized. Their affinity for IGFs is comparable to that of the IGF-I receptor. IGFBPs serve both as carrier proteins and modulators of IGF bioactivity: they are found not only in the circulation but also in the extravascular space of virtually all tissues. IGFBP-3 is the major IGFBP in the circulation; >90% of IGFs in the intravascular compartment are found in a ternary complex composed of the IGF, IGFBP-3, and another protein known as acid-labile subunit.

Tissue IGF bioactivity is determined not only by circulating levels, but also by local expression of IGFs, IGFBPs, and various proteases that cleave IGFBPs to liberate free IGFs. There is accumulating evidence consistent with the view that expression of genes that influence tissue IGF bioactivity is regulated in parallel with circulating IGF-I level. For example, antiestrogens, which lower circulating IGF-I levels [4], also lower IGF-I gene expression in target organs for breast cancer metastasis [5] and stimulate expression of IGFBP-3, which can attenuate IGF bioactivity [6]. This raises the possibility that serum IGF-I levels represent a surrogate for tissue IGF bioactivity.

Both the mitogenic and anti-apoptotic [7,8] effects of IGF-I are mediated by the IGF-I receptor, which is a cell-surface receptor of the tyrosine kinase class [9]. The nomenclature of receptors is somewhat confusing.
PC-3 Xenografts

The IGF-I receptor (also known as the type I IGF receptor) binds both IGF-I and IGF-II. The IGF-II receptor preferentially binds IGF-II, but there is evidence that this 'receptor' does not transduce a mitogenic signal but rather acts as a 'sink' for IGF-II.

There is abundant evidence from both tissue culture and in vivo experimental systems that many neoplasms, including prostate cancer, are mitogenically responsive to IGFs. For example, the growth curves in Figure 1 show reduced proliferation of PC-3 androgen-independent prostate cancer cells in IGF-I deficient \( \text{lit}\text{lit}\) hosts relative to control hosts. The effect of IGF-I is more apparent \textit{in vivo} than \textit{in vitro} for this cell line. The role of IGF physiology in the normal prostate has recently been reviewed [11,12].

**Circulating IGF-I level and risk of prostate cancer**

Several epidemiological studies [13–15] provide data that suggest that prostate cancer is found at higher frequency in men with higher circulating IGF-I levels. The strength of the IGF-I level – prostate cancer risk association is considerable – it is stronger than other risk factors described to date for sporadic prostate
cancer, and is of the same order of magnitude as the association between high serum lipid levels and cardiovascular disease.

Although IGF-I levels are positively correlated with IGFBP-3 levels \( (r \sim .6) \), in multivariate models risk tends to be inversely associated with IGFBP-3 level. This implies that the IGF-I/IGFBP-3 ratio is important, and that particularly high or low risks may be seen in individuals who are outliers on population plots of IGF-I vs. IGFBP-3. This also may explain why there is only a modest excess of cancer in acromegals, who have growth hormone-secreting pituitary tumors: while these individuals have very high IGF-I levels, they also have abnormally high IGFBP-3 levels, and an IGF-I/IGFBP-3 ratio close to normal [16].

In the epidemiological studies to date, most ‘cases’ came to medical attention because of symptomatic prostate cancer, as distinct from identification by clinical or PSA screening. It is not possible from these studies to distinguish between the possibilities that (A) high IGF-I levels are associated with a higher risk of completing early steps of prostate carcinogenesis, or that (B) high IGF-I levels are associated with unchanged risk of completing early steps of prostate carcinogenesis, but a higher rate of neoplastic progression from indolent asymptomatic disease to biologically aggressive and clinically symptomatic disease. Ongoing research similar to the reported epidemiological studies, but defining a ‘case’ as a man with asymptomatic prostate cancer detected by screening examinations may provide useful data in this regard: a finding that serum IGF-I levels are related equally to risk of occult prostate cancer and symptomatic prostate cancer would favor the first possibility, while a finding that IGF-I levels are related to risk of symptomatic prostate cancer but not occult prostate cancer would favor the second.

Why are circulating IGF-I levels related to risk of prostate cancer?

Ongoing research raises the possibility that several common epithelial malignancies besides prostate cancer may be increased in individuals with high IGF-I/IGFBP-3 ratios [17–19]. Therefore, the mechanisms involved may not be prostate-specific. It is unlikely that serum levels of IGF-I or IGFBP-3 directly determine risk: we have proposed that they may be surrogates for tissue IGF bioactivity, which may be a determinant of turnover rate of normal renewing epithelial cell populations. One result consistent with this possibility is provided by recent work comparing proliferation rate of prostate epithelial cells in the normal and IGF-I deficient \( \text{lit/lit} \) mouse. As the baseline turnover rate in the prostate is lower than that in tissues often used for proliferation studies (such as intestinal epithelium), we used a sensitive BrdU labeling technique that involved 120h \( \text{in vivo} \) exposure of mice to BrdU administered continuously by osmotic mini pump to a total dose of 70 \( \mu \text{g/g} \) of body weight. As shown in Figure 2, there is clearly less proliferation marker labeling of prostate epithelial cells in the IGF-I deficiency condition as compared to control.

If higher IGF-I levels are indeed correlated with higher rates of epithelial cell proliferation and/or lower rates of apoptosis, then separate evidence that, provided DNA repair capacity, cell type, and mutagenic insults are held constant, the risk of transformation within a cell population increases with proliferation rate [20–24] becomes relevant, and provides a link between IGF-I level and risk of neoplasia.

Another possibility that may be operative is that higher IGF-I bioactivity may accelerate proliferation and clonal expansion of partially transformed epithelial cells. This would increase the number of cells available for second (or subsequent) hits, and thereby accelerate the accumulation of somatic cell mutations leading to full transformation.

If these concepts prove to be valid, then one might propose that genes expressed in the host (as distinct from the target cells for transformation) that favor increased baseline proliferation are members of a group of ‘host oncogenes’, and those that favor decreased baseline proliferation are members of a novel group of ‘host suppressor genes’. Classic oncogenes and suppressor genes are expressed (or silenced) within the somatic cells that are candidates for transformation. ‘Host’ transforming or suppressor genes, on the other hand, are not expressed within the target cells, but influence the probability of target cell transformation by influencing the environment of the cells (in the current example by leading to an environment for target cells that favors proliferation over apoptosis). Such ‘host’ genes might well influence cells of more than one target organ. We postulate that polymorphic variation of such ‘host’ genes might effect probability of transformation. Decades of exposure to a ‘higher risk’ microenvironment could translate to increased risk of transformation of the order of magnitude observed in recent epidemiological studies [13–15]. There are
Figure 2. \textit{In vivo} proliferation of normal prostate epithelial cells in control and IGF-deficient mice. Mice were exposed to BrdU as described, and prostate tissue was stained for this proliferation marker. Left, control. Right, IGF-I-deficient \textit{lit/lit} mouse. The decrease in number of labeled cells associated with IGF-I deficiency is apparent.

many genes that are involved in regulating IGF-I levels (for example, GHRH, GHRH receptor, growth hormone, etc.), and polymorphic variation of any of these might be associated with variation of IGF-I levels (and risk of prostate cancer). Recent work [25,26] raises the possibility that polymorphisms in the promoter region of the IGF-I gene itself may be important in this regard.

IGF physiology and neoplastic progression

There is evidence that in the process of neoplastic progression, activation of autocrine IGF-II loops is a common event. One (of many) recent examples is the observation by the Vogelstein lab, using SAGE methodology, that the two mRNAs most over expressed (by far) in colorectal cancer cells relative to normal colon epithelium are IGF-II and an IGF-II splice variant [27]. This may in some cases be associated with loss of imprinting of the IGF-II gene [28]. After such events have occurred, one would predict that variability in host IGF physiology would become irrelevant, as the neoplastic cells would be autonomous with respect to ligands for the IGF-I receptor. Analogous studies are underway with prostate tissue.

Another factor which we predict may be associated with neoplastic progression is the expression of IGF binding protein proteases. In the tumor microenvironment, these would tend to increase IGF bioactivity by cleaving IGFBPs and liberating free IGFs. Prostate specific antigen is in fact a proteolytic enzyme that cleaves IGFBP-3 in extracellular fluid, but it is enzymatically inert in the circulation due to the presence of circulating protease inhibitors [29]. It is possible that PSA expression is common in prostate cancer because of clonal selection for the secretion of this enzyme fairly early in the process of transformation.
An important aspect of neoplastic progression concerns the evolution from an androgen-dependent to an androgen-independent phenotype. We have already discussed above the changes in local IGF physiology associated with androgen deprivation therapy of androgen-dependent cancers. An active current area of investigation concerns evaluation of the possibility that progression to androgen independence is also associated with alterations in local IGF physiology.

**Implications for treatment**

Research regarding IGF physiology in prostate cancer is potentially of clinical as well as biological interest. For example, there is recent evidence that current androgen-targeting therapies alter IGF physiology within androgen-responsive cells in a manner that contributes to the apoptosis associated with androgen withdrawal. We have observed massive upregulation of several IGF binding proteins in the prostate following castration, but preceding the onset of castration-induced apoptosis [30]. Similar results have been noted for antiandrogens [31] and growth inhibitory vitamin D analogues [32,33]. Data from these studies are compatible with the view that in androgen-dependent tissues, IGFBP expression is normally suppressed by androgens, and that at the time of androgen deprivation, IGFBP expression rises, leading to a decline in IGF bioactivity which favours apoptotic cell fate, given the recognized anti-apoptotic activity of IGFs [7].

The hypothesis that efficacy of androgen-targeting therapies can be improved by combining them combined with IGF-I targeting therapies is under active investigation. Benefits of such an approach would be expected to be more apparent in the clinic in adjuvant treatment settings as compared to large burden metastatic disease. Clinical trials in the setting of initial adjuvant treatment of prostate cancer and/or following response to androgen ablation are being considered. The first generation of analogous combination adjuvant clinical trials in breast cancer are already underway [34–36].

Other approaches under investigation are listed in Table 1. On theoretical grounds, one might expect GHRH antagonists and somatostatin analogues to be active in relatively well differentiated cancers: since the proposed mechanism involves suppression of host IGF-I levels, they would have minimal impact on tumors with an autocrine source of ligand for the IGF-I receptor. However, recent work shows unexpectedly strong activity of GHRH analogues in models of aggressive prostate cancer, raising the possibility of novel mechanisms of action mediated by GHRH receptors on neoplastic cells, including (surprisingly) inhibition of IGF-II expression [37].

Small molecule inducers of IGF binding protein expression or inhibitors of IGFBP proteolysis might have activity even for tumors with autocrine loops, as would various approaches that target the IGF-I receptor itself [38,39].

Also under investigation in our lab and others is the concept that efficacy of cytotoxic chemotherapeutic agents that induce apoptosis might be enhanced by co-administration of agents that diminish IGF-I bioactivity, given the anti-apoptotic properties of IGF-I. This line of investigation has been stimulated by the results of analogous preclinical studies (and subsequent clinical trials) [40–42] that demonstrate enhanced efficacy of cytotoxic drugs in the presence of blockers of the HER2 receptor.

**Implications for prevention**

As we [13] and commentators [43] have discussed, recent epidemiological observations linking IGF-I to risk of prostate cancer may have implications for future prevention strategies. It must be emphasized that, in contrast to tumor markers such as PSA, serum IGF-I

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<th>Table 1. Novel IGF-targeting therapeutic approaches for prostate cancer under investigation</th>
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level does not originate from neoplastic tissue, and is not a tumor marker. Rather, it represents a host characteristic that appears to be related to the probability of future neoplasia. IGF-I levels fluctuate little over time relative to other hormones.

One simple suggestion is that men with high IGF-I levels (perhaps the top quintile) might benefit from enhanced screening procedures, including PSA screening. In countries where PSA screening is not common, it has been proposed that a single IGF-I measurement might be used to define a subset of the population for whom annual PSA screening might be worthwhile.

It is premature to propose intervention studies that would study potential benefits of pharmacological reduction of IGF-I levels from high-normal to mid-normal values. However, there are a number of points of interest in this regard. First, the concept of pharmacological measures to reduce risk is now well established, with FDA approval of tamoxifen for breast cancer risk reduction in women with specified risk profile, and with an ongoing large prostate cancer prevention trial evaluating an androgen-targeting approach [44]. Second, long-term safety data are available for somatostatin analogues, which are one of several candidate molecules that reduce IGF-I level. However, in acromegalic patients, somatostatin analogues are effective in lowering IGF-I levels from abnormally high towards the normal range; less data are available concerning their potential to lower levels from the ‘high normal’ to ‘mid-normal’ range. It is possible that dose-response relationships might be influenced by pre-treatment IGF-I level. It is to be noted that there is no rationale for proposing to lower levels to below the normal range for the purpose of prevention – the goal would simply be to shift men from ‘high normal’ to ‘low normal’. Finally, while it is unlikely that the current monthly depot formulations would be optimum for long-term use, development of orally-active IGF-I suppressing drugs is possible.

An attractive aspect of potential IGF-I targeting prevention strategies is that unlike current approaches that target androgen physiology, such strategies would be indicated only for the proportion of the population (perhaps 10–20%) at increased risk specifically associated with high IGF-I level. Different individuals may be at risk for prostate cancer for different reasons, each of which might benefit from a specific risk reduction approach. By analogy with cardiovascular disease, high cholesterol and high blood pressure are both risk factors, and those at risk because of hypertension benefit from the correction of this, but interventions regarding their lipids are not needed.

Of course, the key issue to keep in mind is that it remains a hypothesis that measures that lower IGF-I and/or raise IGF-BP3 would in fact lower risk; this concept is in keeping with recent epidemiological observations, but an intervention trial would be required to address it.

While severe dietary restriction is known to lower IGF-I level [2], practical lifestyle modifications that could be used to lower levels have not been described to date.

While there is no evidence that replacement therapy for the appropriate correction of growth hormone deficiency states is dangerous with respect to prostate cancer, there is concern that decades of over-aggressive replacement therapy that achieves super physiological IGF-I levels may be associated with increased risk.

Conclusion

In the past few years, considerable evidence has accumulated that suggests that the IGF system is involved in the pathophysiology of prostate cancer. Recent data has led to interesting proposals for novel treatment and prevention strategies. These research directions are novel and worthy of investigation. The paradigm of exploiting steroid hormone responsivity of neoplastic cells has led to some of the most effective and widely used treatment and prevention strategies in use today, and it is possible that this paradigm can be extended to certain peptides, including the insulin-like growth factors.

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