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Insulin, insulin-like growth factors and neoplasia

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Over the past decade, dozens of epidemiological studies and laboratory experiments have provided evidence for relationships between insulin-like growth factor (IGF) physiology and neoplasia. Population studies provide evidence for a modestly increased risk of a subsequent cancer diagnosis in subjects with IGF-I levels at the high end of the broad normal range, as compared to those at the low end of the normal range. At the cellular level, IGF-I receptor signalling has been shown to play an important role in facilitating the transforming action of a variety of

history, an ancestral insulin-like receptor Ð rather than a speciÞc insulin receptor or insulin-like growth factor receptor Ð initiated signalling. In higher organisms, as the need arose to regulate cellular proliferation and survival independently of short-term regulation of cellular uptake of glucose, distinct insulin-like growth factor and insulin receptors and ligands evolved.

It is well recognized that IGF-I receptors are widely distributed in normal and malignant tissues.[1] (So-called IGF-II receptors do not transduce a signal but serve to restrain growth by competing with IGF-I receptors for IGF-II; IGF-II is commonly over-expressed in cancer, and accordingly the gene encoding the IGF-II receptor has the properties of a tumour suppressor gene.[5Ð7]) Classic insulin-sensitive tissues include muscle, liver, and fat, and these tissues display insulin receptors. Less well studied is the role of the insulin receptor present on normal and transformed epithelial cells.[8] While insulin receptors may be involved in regulation of glucose uptake by epithelial cells, epithelial tissues comprise a small proportion of body weight relative to the total weight of liver, muscle, and fat, so these tissues probably play only a minor role in disposing of circulating glucose.

Most common cancers arise from epithelial cells, and express both the gene encoding the insulin receptor and the gene encoding the IGF-I receptor.[8] This leads to a situation where not only insulin and IGF-I receptors but also hybrid receptors (composed of a Ôhalf insulin receptorÕ and a Ôhalf IGF-I receptorÕ) are expressed on the cell surface.[9] In general terms, hybrid receptors appear to have higher afÞnity for IGF-I and IGF-II than insulin. There are important gaps in knowledge concerning the relative expression levels of insulin receptors and IGF-I receptors by cancer cells. Furthermore, the signiÞcance of the relative expression levels of the two insulin receptor isoforms requires clariÞcation. The IR-A insulin receptor isoform, which appears to have afÞnity for IGF-II, could be involved in IGF-II autocrine loops, which are commonly seen in neoplastic tissue, and which were previously thought to involve exclusively the IGF-I receptor.[8,10]

Ligands

The microenvironment of normal cells at risk for transformation and of cancer cells contains insulin, IGF-I, and IGF-II. With rare exceptions,[11] insulin is not produced by cancers. In contrast, substantial IGF-I and/or IGF-II is locally produced by neoplastic

that are produced locally within the target tissue as well as in the liver. While epidemiological research regarding the inßuence of insulin on cancer is less hampered by this issue than studies of IGFs, studies of insulin have other challenges related to the imprecision of using random or even fasting or postprandial measurements to estimate the impact of levels that ßuctuate throughout the day according to nutrient consumption.

LABORATORY STUDIES

Laboratory studies regarding roles of insulin in neoplasia preceded those concerning roles of the IGFs. Early studies not only showed that insulin at physiologically relevant concentrations stimulates DNA synthesis in breast cancer cells[17] but they also provided early evidence that insulin deÞciency is associated with less aggressive cancer proliferation in vivo.[18] Until the recent resurgence of interest,[19] however, little attention was given to following up on these observations made more than 20 years ago, probably because of the assumption that any attempt to reduce insulin signalling would have grave metabolic consequences.

IGF-I receptor targeting strategies were Þrst proposed over 20 years ago, when IGF-I receptors were detected on human cancers.[20] Many subsequent in-vitro and in-vivo models, when viewed as a whole, provide convincing evidence for a role for the IGF-I receptor in neoplasia. A comprehensive listing of all studies in the literature is beyond the scope of this review, but key examples will be highlighted. Early in vitro experiments demonstrated dose-dependent increases in neoplastic cell proliferation with increasing IGF-I concentration.[21] In-vivo models made use of naturally occurring mutations associated with low IGF-I levels[22] or genetic manipulations[23,24] to inßuence ligand levels to show that, in vivo, tumour growth is inßuenced by host IGF-I physiology. More recently, several drug candidates that target IGF-I signalling were found to have anti-neoplastic activity TJ T3phlil severah 2(inßuenc)-7(e)]TJ -30.012 -3212 o

cancer diagnosis than those at the low end of the normal range. Some of these early reports also described a Þnding that higher circulating levels of IGFBP-3 were associated with reduced risk, which was interpreted as reßecting an inßuence of IGFBP-3 as reducing IGF-I bioactivity, in keeping with laboratory studies.[43,44] However, some follow-up studies (for example that of Schernhammer et al.[50,51]) have failed to conÞrm these reports, or have revealed weaker relationships.

In considering these inconsistencies, it is worthwhile reßecting Þrst on the underlying biology and then on methodological issues. Why might circulating IGF-I levels be related to cancer risk in the Þrst place? Two hypotheses are worth considering. One suggests that early in carcinogenesis, as somatic cell mutations lead to accumulating DNA damage in an at-risk cell, the IGF bioactivity in the cellular microenvironment is a critical factor that inßuences the fate of the cell: will it survive and evolve to a frankly malignant cell lineage, or will it undergo apoptotic death? Given that IGF-I receptor activation activates pro-survival signalling pathways,[51] the balance between apoptotic cell death versus survival of damaged cells might be slightly tipped towards survival in a Ôhigh IGFÕ environment, and this would favour the emergence of a malignant clone. Many other factors also inßuence this process, but over many years, and recognizing that the fate of millions of DNA-damaged cells is determined every hour, even a modest inßuence of higher IGF-I level on survival probability might lead to an association of circulating level with cancer risk.

A second hypothesis suggests that the inßuence of IGF-I level on cancer risk has little to do with early carcinogenesis. This view suggests that higher IGF-I levels simply favour the more rapid proliferation of early cancers to the point at which they are clinically detectable. This hypothesis would predict that if one had a means to detect 1-mm tumours, the number of these lesions would be unaffected by IGF-I levels. Rather, such lesions would be common in all adults, and risk of a clinical cancer diagnosis would reßect the probability of these lesions progressing toward a detectable and clinically signiÞcant size, with this latter process being inßuenced by IGF-I level. Findings in the case of prostate cancer may be consistent with this second hypothesis. First, autopsy studies show that undetected prostate cancers are very common, and present in the majority of adult men.[52] Second, there is evidence that diagnosis of prostate cancer years after a baseline IGF-I level is obtained is more closely associated with this baseline level in a population without PSA screening than one with PSA screening.[46,47] This is consistent with the view that the IGF-I level is more related to the probability of progression of early lesions than to the process of early carcinogenesis. Both hypotheses are plausible. They are not mutually exclusive. There is no deÞnitive mechanistic evidence to support either of them.

Why are there inconsistencies among studies relating cancer risk to IGF-I level? One possibility is that the problem is technical. The measurement methodologod0 Td [-39
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but it is not of use in clarifying the cause of chest pain. High cholesterol indicates an environment where cardiac disease is more likely to develop, but does not represent direct evidence of the disease. Similarly, IGF-I levels that are in the high end of the normal range do not represent evidence of the presence of cancer, but rather may reßect a host characteristic that may indicate a relatively favourable environment for carcinogenesis and/or neoplastic progression.

However, it is also plausible that some of the inconsistencies in the literature result from biological factors. Perhaps IGF-I levels are only related to risk in speciÞc subsets of patients, and variation i**n**modifying factors

as metformin[64–67] might be beneficial. This area is under intense investigation by many groups. Obesity is associated with excess cancer mortality[68] and this may be mediated at least in part by obesity-associated hyperinsulinism, so this topic has potential public health relevance.

CLINICAL IMPLICATIONS

Cancer risk

The detection of a relationship between circulating IGF-I levels and risk of a subsequent diagnosis of certain common cancers is intriguing, but does not have major clinical relevance at present. The increased risk associated with high-normal as compared to low-normal IGF-I levels is very much less than the risks associated with smoking or with inherited cancer predisposition syndromes. Furthermore, there is no obvious specific prevention strategy to offer to those with IGF-I levels in the high-normal range. It is occasionally stated that reduction of caloric intake and/or increased exercise might be particularly beneficial for those with high IGF-I levels, but this is speculation rather than evidence-based advice. There is a possibility that future research will show that attempts to devise global cancer risk assessment tools will include IGF-I levels as one of the predictive variables, and there is also considerable interest in the possibility that IGF-I serum levels may interact with or modify the impact of genetic risk, such as *BRCA1* mutation. However, these topics remain in the research domain at present.

Does the accumulated evidence have implications for growth hormone or IGF-I replacement therapy? This is an area of controversy[69], but it is rational to speculate that achieving levels of IGF-I in excess of age-specific norms, particularly if maintained indefinitely, might stimulate growth of any existing cancers. This can lead to a clinical recommendation to avoid GH therapy in the setting of a diagnosed cancer. However, as most cancers are believed to have a long latency period before becoming clinically

Cancer treatment

As a result of the evolving consensus for a role of IGF signalling in neoplasia[1], the pharmaceutical industry has undertaken many drug development projects to develop agents that target this pathway. These include anti-ligand and anti- receptor approaches.

Anti-ligand approaches

The earliest anti-ligand approach involved efforts to reduce IGF-I levels by the use of somatostatin analogues[71]. This approach has now been shown to be ßawed. Despite evidence for preclinical activity[72], it was shown in a long-term clinical trial that in non-acromegalic subjects, tolerance develops to the GH- and IGF-I-suppressing properties of the somatostatin analogue octreotide, so the lack of an important inßuence on cancer endpoints[71] should not come as a surprise. More recently, anti-ligand antibodies that cross-react with IGF-I and IGF-II have been developed, and these show impressive activity in preclinical cancer models[25], but these have not been evaluated in the clinic.

Anti-receptor antibodies

There is major interest in targeting IGF-I receptors with anti-receptor antibodies, and

BMS.[26] Clinical trials of these agents are at an earlier stage than those of the IGF-I

Practice points

- growth hormone and IGF-I are not carcinogens; nevertheless, in situations where there is a clinical indication for their use in the treatment of deÞciency states, the goal should be to achieve replacement levels no higher than physiological
- the use of growth hormone or IGF-I is not recommended for patients with cancer
- although there is evidence for a modest increase in cancer risk among subjects with higher circulating IGF-I levels, pharmacological reduction of GH or IGF-I levels for the purpose of cancer risk reduction has not been the subject of clinical trials and is not currently recommended.

Research agenda

- more than a dozen new drugs designed to reduce signal transduction through the IGF-I receptor (and/or the insulin receptor) are now being evaluated to determine whether they have signiÞcant anti-neoplastic activity for various different cancers, either alone or in combination with other drugs; this area of research has become one of the most active research areas at the interface between oncology and endocrinology
- although there is considerable circumstantial evidence that implicates hyperinsulinaemia as a mediator of the adverse effect of obesity on cancer prognosis, this remains to be formally demonstrated; more studies on the relationship of the inßuence of the Ômetabolic syndromeÕ on cancer risk and prognosis are needed
- one speciÞc area of interest concerns prostate cancer, where androgen-deprivation therapies result in hyperinsulinaemia: does this secondary endocrine effect,95(cir)15 -1eprs7olsReyelaigni i(orTD (2)7ign T* [aret1 0nc)-7(ep412(Ñ2(with)-33n

SUMMARY

Taken together, laboratory and epidemiological Þndings provide convincing evidence that insulin and IGF-I physiology are relevant to neoplasia. Higher IGF-I levels in the circulation have been associated with moderately increased risk of a subsequent diagnosis of several common cancers, but there is limited clinical application of this information at present. In contrast, the potential clinical relevance of evidence that IGF-I signalling in cancer cells contributes to neoplastic behaviour is now being evaluated by over 20 clinical trials involving several drug candidates. Furthermore, there is increasing interest in the evidence that hyperinsulinism leads to adverse prognosis

among cancer patients; this has led to ongoing investigations of the concept that drugs such as metformin may be of value as adjunctive treatment in the substantial subpopulation of cancer patients who are hyperinsulinaemic.

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