4 Insulin-Like Growth Factor-Related Signaling and Cancer Development

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Abstract

In this review, selected examples of recent research developments concerning insulin-like growth factors (IGFs) and insulin in the context of cancer risk assessment and prevention will be discussed. We reviewed background information related to IGF physiology at the cellular and whole-organism levels, together with prior work concerning IGF-I levels and risk of a variety of cancers, including breast, prostate, colon, and lung in 2004 (Pollak et al. 2004). A comprehensive update to that general review (Pollak et al. 2004) is scheduled for Nature Reviews Cancer in early 2007.

General Background Issues Concerning Cancer Risk Assessment

Individuals are distinct from each other not only regarding their level of cancer risk, but also with respect to the dominant mechanism underlying their risk. As an example related to breast cancer, consider five women: a carrier of a BRCA1 mutation, a woman who started to menstruate at age 9, a woman with high birthweight, a woman with high mammographic density, and a woman with radiation exposure at puberty. All are at increased risk relative to women without identified risk factors, but because the mechanism responsible for increased risk is distinct in each case, one cannot presume that any specific risk reduction strategy will benefit each woman to the same degree. A panel of ideal serum or DNA markers of risk would not only quantify magnitude of risk, but would also provide information regarding the mechanism underlying the increased risk; this would be useful in selecting a particular risk reduction strategy that is effective for the risk mechanism involved.

At present, markers of risk fall short of this ideal. For example, mammographic breast density is known to be associated with increased risk, but because the mechanisms that link density to risk are poorly understood, there is no standard risk reduction strategy recognized as particularly appropriate for these women. Risk reduction strategies that have been studied in major clinical prevention trials, such as tamoxifen, are known to reduce breast cancer risk, but we do not understand clearly for which women such interventions are most effective. While risk reduction on the order of 40% has been reported for women taking tamoxifen as a chemopreventive, it is unlikely that all women in tamoxifen prevention trials derived a similar degree of protection: based on the varying molecular pathology that is responsible for risk in individual women, some may have enjoyed a 90% risk reduction with tamoxifen, while others may have derived no benefit. An important research goal is to develop markers of risk that would both quantitate risk and allow rational selection of an appropriate intervention for an individual woman.

Another general issue concerns definition of cancer prevention. Recent work (Thompson et al. 2003, 2004) supports prior studies that suggested that early steps of malignant transformation are common by middle age, particularly in organs such as breast and prostate. In the case of prostate, even histologically invasive cancer that is clinically silent is common (Thompson et al. 2003, 2004). Obviously, prevention interventions that are clinically useful are those that prevent

clinically important disease. Such prevention interventions may not have to act to limit early carcinogenesis in all cases (this would imply the need for interventions relatively early in life), but rather may act to inhibit neoplastic progression of early lesions. This point has implications for development of markers of risk: for a disease such as prostate cancer, which is now recognized to be present in a large proportion of the adult male population (Thompson et al. 2003, 2004), prevention of clinically important disease may be aided more by discovery of markers of probability of progression than markers that indicate the presence of early disease or markers that indicate risk of developing early disease.

IGF-Related Serum Markers and Prostate Cancer

The first prospective study (Chan et al. 1998) that linked circulating IGF-I levels to risk of prostate cancer was reported in Science in 1998, and generated considerable interest in the field, both in terms of population and laboratory (e.g., Majeed et al. 2005) studies. However, the study was small (only 152 cases and 152 controls), and there was little information regarding the nature of the prostate cancers that were found at increased frequency among those men with higher IGF-I levels (especially if these levels were associated with a relatively low level of IGFBP-3, the major serum IGF-binding protein). Subsequent studies and a meta-analysis (Renehan et al. 2004) confirmed the association of IGF-I levels with increased risk of a subsequent diagnosis of prostate cancer. It should be emphasized that these studies did not establish IGF-I as a tumor marker for prostate cancer: to use an analogy from cardiology, higher levels of IGF-I were found to be indicative of increased risk of a later diagnosis of prostate cancer, as elevated cholesterol indicates increased risk of a subsequent myocardial infarction. However, cardiologists do not measure cholesterol to make a diagnosis of myocardial infarction in a patient with chest pain, and a measurement of a high IGF-I level does not indicate the presence of prostate cancer.

Ongoing work (e.g., Ma et al. 2005), is seeking to extend earlier results concerning the relationship between IGF-I and prostate cancer risk by studying larger numbers of cases and controls, in order to determine if men with higher IGF-I levels are at risk for any particular subtype of prostate cancer. This work is complicated by changes in patterns of PSA screening in study populations. In older work, many cases were not detected by screening, but rather were men who presented with symptoms of prostate cancer; these men obviously had more advanced disease as a group than men with prostate cancer detected by screening. In later series, particularly those from North America, many subjects classified as prostate cancer cases had relatively early prostate cancer detected by screening. There is now emerging evidence from prospective study populations that higher levels of IGF-I (particularly when associated with relatively low levels of IGFBP-3) may in fact be specifically related to risk of a subsequent diagnosis of advanced or poor prognosis prostate cancer, while IGF-I (and IGFBP-3) levels are not associated with risk of a subsequent diagnosis of localized, good-prognosis disease.

This area of research clearly deserves further attention, because of two important unmet clinical needs. In a screening context, a marker associated with probability of developing advanced disease would aid in clinical decision-making when a screening exercise detects an early cancer – together with currently used criteria such as the Gleason score, such a marker might aid in making decisions for (or against) watchful waiting in individual cases. In a prevention context, subtly distinct from the screening context, given the very common presence of early prostate cancer lesions in adult males, a case could be made that all men with a high probability of developing more advanced prostate cancer (regardless of whether they have a current prostate cancer diagnosis) could be considered candidates for a prevention strategy that acts by reducing likelihood of progression of early cancers.

IGF-Related Markers and Breast Cancer Risk

One of the earliest prospective studies concerning IGF-I serum levels and subsequent risk of

breast cancer (Hankison et al. 1998) reported that IGF-I levels were strongly related to risk of premenopausal, but not postmenopausal breast cancer. Several subsequent studies (e.g., Toniolo et al. 2000) reached similar conclusions, but there has been inconsistency in the literature, with some recent negative studies (e.g., Rinaldi et al. 2005; Schernhammer et al. 2006). The reason for this inconsistency is under investigation. The initial positive studies may simply have been chance findings, but it is also possible that there is an undiscovered modifying factor that influences the relationship between IGF-I level and risk. For example, cohorts or subcohorts with higher BMI or insulin levels might show a higher overall risk level than other cohorts, and such increased risk might well obscure any effect of IGF-I. While this explanation is plausible and deserves exploration, to date no data explain the inconsistencies that have been presented.

It is also possible that IGF-I levels sampled at younger ages are more related to later risk of breast cancer (Rollinson et al. 2005) than levels in samples obtained later in life. This is plausible because there is precedent for breast cancer risk factors that act mainly during a vulnerable period around the time of puberty to influence lifetime breast cancer risk. Although it has been assumed that individuals stay true to their centile of breast cancer throughout life (i.e., being in the top decile of the population at age 45 implies one was at the top decile at age 15), this has never been verified, as sample sets obtained from subjects repetitively sampled over decades are rare.

There is reasonably strong laboratory evidence (e.g., Pollak et al. 2001) that is consistent with the original reports of a positive association with risk. Furthermore, there is interesting circumstantial evidence consistent with the original observations from several reports linking mammographic breast density, a known strong breast cancer risk factor, to IGF-I and IGFBP-3 levels (Diorio et al. 2005, 2006; Byrne et al. 2000; Maskarinec et al. 2003). Additional circumstantial evidence comes from work relating birth weight and preadult growth patterns (both known to be influenced by IGF physiology) to breast cancer risk (Ahlgren et al. 2004).

Finally, a recent report on one of the largest sample sets studied to date (Al-Zahrani et al. 2006) did reveal a modest positive association between IGF-I levels and risk, and also extended prior work (Deal et al. 2001) by providing data showing that specific polymorphisms in genes encoding proteins involved in IGF-I physiology were related to both circulating levels and to risk of breast cancer.

Obesity, Insulin, Risk of Cancer, and Risk of Aggressive Cancer

Metabolic host risk factors or host prognostic factors (as distinct from better described tumor factors such as PTEN deletion or HER2 amplification) can influence the natural history of cancer. There is increasing evidence that obesity is related to increased risk of and/or worsened prognosis of many common kinds of cancer (Calle et al. 2003). The molecular and endocrinologic mechanism(s) underlying this relationship are the subject of ongoing research in many laboratories. This research is important because in view of the fact that obesity is becoming increasingly common around the world, there is concern that there may be a secondary effect of increased frequency of cancer diagnosis, and/or more aggressive behavior of cancers in populations.

Obesity and excess caloric intake are associated with many metabolic changes, including, for example, elevations of circulating insulin and leptin levels. Elevated insulin levels can increase IGF bioactivity by suppressing expression of certain IGF-binding proteins, particularly IGFBP-1. Elevated insulin levels might also directly stimulate neoplastic cell proliferation and survival by activating receptors on cancer cells that are upstream from the AKT survival signaling pathway. More studies are needed, however, to clarify with precision the receptors involved. Physiological levels of insulin, even if elevated in the context of obesity, are likely insufficient to activate IGF-I receptors directly. It is possible that certain neoplastic cells exhibit insulin receptors and/or hybrid insulin-IGF receptors that could respond to levels of insulin found in obese patients. At present, the possibility that the adverse influence of obesity could involve increased signaling downstream of insulin and/or insulin receptors is a

plausible but unproven hypothesis. Advances in our understanding will require both laboratory models and clinical research. Early clinical results are consistent with the hypothesis (Wei et al. 2005; Ma et al. 2004; Schairer et al. 2004).

An interesting related point concerns the drug metformin, which has been in extensive use in the management of type II diabetes for many years. This drug is known to lower the elevated insulin levels found in type II diabetes, but to have little effect when given to people with normal insulin levels. Although there was a prior hypothesis that metformin acted as a sensitizer of cells to insulin action, and that this accounted for the drop in insulin level, recent evidence suggests that the drug acts primarily in vivo by reducing glucose output by the liver (gluconeogenesis) and that the fall in circulating insulin level is secondary to the fall in glucose (Shaw et al. 2005). Interestingly, the molecular pathways involved in this action of metformin in the liver involve activation of the amp-kinase/lkb1 tumor suppressor pathway. Specifically in hepatocytes, this pathway shuts off glucose output (Shaw et al. 2005). However, we have shown in ongoing laboratory studies that for some cancer cell lines, metformin acts as a growth inhibitor specifically by activating the same ampk/lkb1 tumor suppressor pathway. In these cell lines, as expected on the basis of studies of the LKB1/ampk pathway, metformin-induced ampk activation results in growth inhibition at the level of m-tor. In a sense, metformin may act by simulating low cellular energy supply, and thereby activating the physiologic control systems that presumably have evolved to block or at least dampen the action of mitogenic signals if there is not sufficient energy available for cell division.

Thus on theoretical grounds, metformin might act in two ways to constrain abnormal cell growth: (a) in vivo, it could reduce direct action of insulin or insulin-dependent mitogenic signals through its action as an insulin-lowering agent, and (b) it might have a direct growth inhibitory role by stimulating the lkb1/ampkinase tumor suppressor pathway. These mechanisms are not mutually exclusive, but research in this area is in its infancy, and much more work is needed to evaluate the actions of metformin. Nevertheless, it is tempting to speculate that this old drug or new derivatives might find new uses in the context of cancer prevention, particularly among obese individuals. Two recent studies provide further motivation for studies in this area: one report provides early evidence that the death rate from cancer is lower among diabetics taking metformin than diabetics on other treatments (Bowker et al. 2006), while the other reports that a cancer diagnosis is less common among metformin users than other diabetics (Evans et al; 2005).

Conclusion

The field of IGF and insulin signaling in relation to cancer risk and prevention remains an active research area for laboratory scientists, clinicians, and population scientists. While interesting new experimental and population studies have been reported, substantial gaps in basic knowledge remain to be filled before the possibility of potential clinical applications can be addressed.

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