Minireview: IGF, Insulin, and Cancer

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In recent years, the influence of the IGF system and insulin on cancer growth has been widely studied. Observational human studies have reported increased cancer mortality in those with obesity and type 2 diabetes, which may be attributable to hyperinsulinemia, elevated IGF-I, or potentially both factors. Conversely, those with low insulin, IGF-I and IGF-II levels appear to be relatively protected from cancer development. Initial attention focused on the role of IGF-I in tumor development. The results of these investigations allowed for the development of therapies targeting the IGF-I receptor signaling pathway. However, after *in vitro* and *in vivo* studies demonstrating that insulin may also play a significant and independent role in tumorigenesis, insulin is now receiving more attention in this regard. Some studies suggest that targeting insulin receptor signaling may be an important alternative or adjunct to targeting IGF-I receptor signaling. In this minireview, we discuss some of the recent *in vitro*, animal, and clinical studies that have elaborated our understanding of the influence of IGF and insulin on tumorigenesis. These studies have shed more light on the interaction between insulin and IGF signaling in cancer cells. They have made possible the development of novel targeted therapies and highlighted some of the potential future directions for research and therapeutics. **(*Endocrinology* 152: 2546–2551, 2011)**

"We know many interesting effects of insulin, but we have much to learn before the picture is complete," were the words of Charles Best in the Banting Memorial Lecture of 1945 (1). At the time of its discovery in 1922, insulin was hailed as the "cure" for diabetes. Almost 90 years on, reports that higher endogenous insulin levels and insulin analogs are linked to an increased risk of cancer have once again placed insulin in the spotlight. The recent concern about insulin and cancer stemmed from epidemiological studies reporting that insulin therapy and insulin secretagogues may increase cancer risk (2, 3). Before the publication of these articles, epidemiological studies reported that obese individuals and those with type 2 diabetes were at a higher risk of dying from various cancers when compared with those with a normal body mass index and those without diabetes (4, 5). Insulin resistance in metabolic tissues, such as muscle, liver, and adipose tissue, occurs in obesity and type 2 diabetes. In an attempt to overcome the peripheral insulin resistance, a compensatory hyperinsulinemia develops (6). Some cancer cells have increased insulin receptor (IR) content, and in the setting of hyperinsulinemia, certain tumors may demonstrate increased activation of IR signaling pathways (7, 8). The roles of the closely related IGF-I, IGF-II, and their receptor interactions in cancer have also been extensively studied. Insulin indirectly increases hepatic IGF-I production (9, 10). In addition, hyperinsulinemia may increase the quantity of bioavailable IGF-I by directly or indirectly decreasing levels of IGF binding protein (IGFBP)-1 and IGFBP-3 (11, 12). Lower levels of these binding proteins result in more unbound IGF-I that is free to interact with the IGF-I receptor (IGF-IR). Additionally, many tumors overexpress IGF-II, which also signals through the IGF-IR and one of the IR isoforms, IR-A (13–16). Uncovering the interplay between insulin, IGF-I, IGF-II, IGFBP, the IR, IGF-IR, and their signaling pathways has created a more elaborate illustration of the effects of insulin since the Banting Lecture of 1945. However, even now, much re-

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Abbreviations: cIGHD, Congenital isolated GH deficiency; GHRD, GH receptor deficiency; IGFBP, IGF binding protein; IGF-IR, IGF-I receptor; IR, insulin receptor; PI3K, phosphatidylinositol 3-kinase pathway.

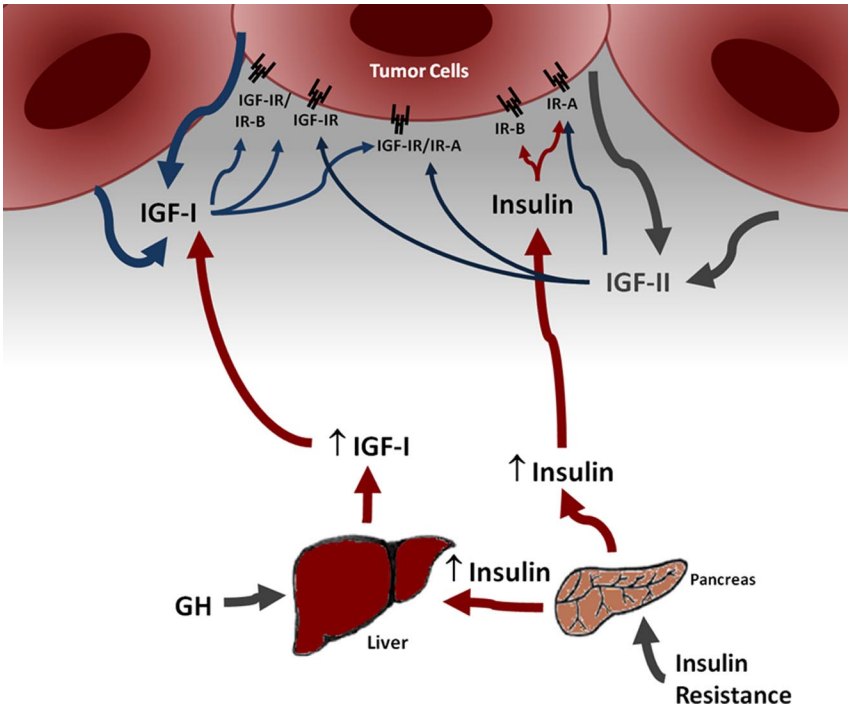

FIG. 1. Endocrine, autocrine, and paracrine signaling of insulin, IGF-I, and IGF-II in tumor cells. Schematic representing the effect of insulin resistance on endocrine production of insulin and GH effect on hepatic IGF-I production as well as autocrine and paracrine production of IGF-I and IGF-II by tumor cells. *Arrows* from insulin, IGF-I, and IGF-II demonstrate their interactions with the IR isoforms (IR-A and IR-B), the IGF-IR, and the hybrid receptors (IGF-IR/IR-A and IGF-IR/IR-B).

mains to be learned to complete the picture. In this minireview, we will discuss in further detail some of the recent studies and the current understanding of insulin, IGFs, their receptors, and signaling pathways in cancer development.

IGF and Cancer

Individuals with increased GH secretion due to acromegaly have elevated IGF-I levels. These individuals have been reported to be at increased risk of colon, breast, thyroid, and prostate cancer, thought to be driven by the proliferative effects of IGF-I (17). Although some epidemiological studies report no relationship between IGF-I levels and cancer risk, many others report that nonacromegalic individuals with IGF-I levels at the upper end of the normal range have an increased risk of developing certain cancers (colon, breast, and prostate) (18–22). Conversely, individuals with GH receptor deficiency (GHRD), also known as Laron syndrome (congenital IGF-I deficiency and GH insensitivity), and individuals with congenital isolated GH deficiency (cIGHD), who also have very low IGF-I levels, appear to be protected from the development of cancer when compared with their relatives without the hormonal deficiency (23, 24). Although the cohort of patients in one of these recent studies was significantly younger than their comparative family members (approximately 18% of those with Laron syndrome and cIGHD were over 30 yr of age) the findings are consistent between both studies and with previous animal studies (23, 24). Caloric restriction in mice leading to a modest reduction (25%) in circulating IGF-I levels reduced bladder tumor growth, by increasing apoptosis and decreasing cellular proliferation (25). Similarly, in the liver-specific IGF-I-deficient (LID) mouse that has very low circulating IGF-I levels, a decrease in colonic and mammary tumors was observed (26, 27). In these animal studies, administration of IGF-I reversed the protective effects of IGF-I deficiency, with restoration of tumor proliferation and decreased apoptosis, ultimately resulting in increased tumor growth and metastasis (26, 27). Notably, in the study of patients with Laron syndrome and cIGHD, previous treatment with IGF-I did not appear to increase a patient's risk of cancer development. However, long-term follow up of these patients is necessary to determine whether or not this will continue to hold true (23).

Alterations in the IGF-I signaling pathway have been described in multiple tumors, including osteosarcomas, gynecological, gastrointestinal, prostate, and lung cancers. Animal and human studies have demonstrated that IGF-I functions not only as an endocrine hormone but also as a paracrine and autocrine hormone, being produced by the tumor cells and interacting with the IGF-IR, which is frequently overexpressed in tumors (Fig. 1) (28–31). Some studies have demonstrated that circulating IGF-I levels do not correlate with tumor progression, whereas increased local IGF-I production by the tumor and IGF-IR expression adversely impact disease prognosis (31).

IGF-II is produced by the liver in human adults, but similar to IGF-I, it is also a paracrine hormone that may be overexpressed in certain tumor cells (Fig. 1) (14, 15, 32). *In vitro* studies have demonstrated that IGF-II has antiapoptotic and proproliferative effects in cell lines. Loss of imprinting and consequent overexpression of the IGF-II gene was initially described in Wilms tumor and Beckwith-Wiedemann syndrome (33, 34). Overexpression of IGF-II has subsequently been described in other gastrointestinal and gynecological tumors (14, 15, 32). Increased IGF-II expression in gastric adenocarcinoma is associated with

reduced disease-free survival (14). Additionally, increased levels of IGF-II expression have been found in the breast cancer tissue of African American women, compared with Caucasian American women. This increased IGF-II expression may endow more aggressive characteristics on the breast cancer phenotypes seen in African American women and partially explain the greater breast cancer mortality seen in African American women, compared with their Caucasian American counterparts (35). The same research group demonstrated that African American women have higher levels of IGF-IR expression in both normal and malignant tissues, compared with the tissue samples of Caucasian American women. In contrast, the Caucasian American women had higher levels of IGF-IIR expression in tumor samples (36). The IGF-IIR clears IGF-II from the cell surface, therefore preventing IGF-II from interacting with the IGF-IR and IR and activating mitogenic signaling pathways. In the previously mentioned population with GHRD, as well as having low IGF-I levels, they were also found to have significantly lower IGF-II levels than their relatives without the GHRD. The lower IGF-II levels in this population are likely due to decreased levels of IGFBP-3 and the acid labile subunit that bind IGF-II and are GH dependent, rather than a direct stimulatory effect of GH on IGF-II production (24). It is possible that this lower level of IGF-II may also be conferring some protective effect against cancer development in this population.

IGF-IR and Cancer

The IGF-IR is a tyrosine kinase receptor, similar in structure to the IR. Both the IR and IGF-IR are made up of an α-subunit and β-subunit, linked to another α- and β-subunit by disulfide bonds. IGF-I and IGF-II bind to the α-subunit of the IGF-IR, leading to autophosphorylation of the β-subunit and consequent activation of intracellular signaling pathways: the MAPK pathway, the phosphatidylinositol 3-kinase pathway (PI3K), or the Janus kinase/signal transducer and activator of transcription pathway (JAK/STAT). The result of activating the MAPK pathway is increased cellular proliferation, whereas activating the PI3K pathway inhibits apoptosis and stimulates protein synthesis, and the Janus kinase/signal transducer and activator of transcription pathway activates gene transcription and may be responsible for the transforming activity of the IGF-IR (37–40). In addition to forming the IGF-IR from two α- and β-subunits, one α- and β-subunit from the IGF-IR may also form hybrid receptors with one α- and β-subunit from the IR. There are two IR isoforms, formed by alternative splicing of exon 11: IR-A, which lacks exon 11, and IR-B, which contains exon 11. Insulin binds to IR-A, IR-B, or the IGF-IR but binds to the IGF-IR with much lower affinity than to the IR; it does not bind to the hybrid receptors. IGF-I binds to the IGF-IR, hybrid receptors, or IR but has a much lower affinity for the IR than IGF-IR. IGF-II binds to the IGF-IR, IR-A, and the IGF-IR/IR-A hybrid receptor (Fig. 1). Phosphorylation of the IGF-IR or IGF-IR/IR-A hybrid receptor by IGF-I or IGF-II binding predominantly leads to mitogenic signaling, phosphorylation of IR-A by insulin or IGF-II binding also leads to mitogenic signaling, whereas activation of IR-B by insulin, or the hybrid IGF-IR/IR-B by IGF-I, results mostly in metabolic signaling (37, 38).

In vitro studies have demonstrated that a functioning IGF-IR is necessary for cell transformation by many viral and cellular oncogenes and appears to be important in expressing the genes that regulate the cell cycle, cell survival, motility, attachment, and metastasis (41, 42). In breast cancer, the IGF-IR is frequently overexpressed and may play a role in mammary cell transformation (43, 44). Animal studies have demonstrated that IGF-IR expression induces tumor growth and metastasis, whereas decreasing IGF-IR expression, leads to decreased tumor growth in the majority of tumors (44). Consistent with the findings of the previously mentioned study comparing breast tissues from African American and Caucasian American women, a case control study from the Nurse's Health Study cohort correlated IGF-IR expression levels in benign breast biopsies with subsequent risk of breast cancer and found that cytoplasmic positive/membrane negative IGF-IR expression is associated with an increased risk of subsequent breast cancer (36, 45). The significance of increased internalization of the IGF-IR is incompletely understood, but the authors suggest that it may reflect changes in the activation status of the IGF-IR (45). In addition, high levels of IGF-IR expression appear to confer tumors with an inherent resistance to radiotherapy and lower patient survival (46, 47). Therefore, targeting IGF-IR signaling has been a desirable option in the treatment of tumors overexpressing the IGF-IR.

There are ongoing phase I–III clinical trials evaluating the safety and efficacy of drugs targeting the IGF-IR (NCT01231347, NCT00924989, and NCT00785538). One such study in patients with sarcoma and Ewing's sarcoma reported that the monoclonal antibody targeting the IGF-IR (figitumumab) was well tolerated with good tumor response (48). Other antibodies target IGF-I and IGF-II, therefore preventing mitogenic signaling of either IGF-I or IGF-II through the IGF-IR and hybrid receptors, as well as signaling of IGF-II through IR-A, but not affecting metabolic signaling through IR-B (49). Interestingly, studies in cell lines have demonstrated that knocking out, downregulating, or pharmacologically inhibiting the IGF-IR

can lead to a compensatory increase in IR signaling (50–53). Due to these findings and the studies suggesting that insulin analogs may promote tumorigenesis, the effect of insulin on tumor growth has recently received greater attention.

Insulin and Cancer

Animal and cell studies have been conducted to investigate the role of insulin in tumorigenesis. In a transgenic mouse model of a pancreatic β-cell neuroendocrine tumor, up-regulation of the IGF-IR accelerated tumorigenesis. However, surprisingly, targeting the IGF-IR with an inhibitory antibody did not greatly reduce tumor growth. Both IR-A and IR-B protein expression were found to be increased in these cells. When the IR expression was suppressed, in addition to blocking the IGF-IR, tumor growth was impeded (51). Additionally, a study on mouse embryonal fibroblasts demonstrated that knocking out the IGF-IR results in increased sensitivity of the IR to insulin at concentrations close to physiological levels (52). This finding raises the concern that blocking the IGF-IR in individuals with insulin resistance, hyperinsulinemia, or diabetes may lead to resistance to IGF-IR-targeted therapy by activation of IR signaling (52, 53). Hyperinsulinemia, in a nonobese mouse model of type 2 diabetes, has been reported to lead to increased mammary tumor growth (8). Again, blocking the IGF-IR and IR tyrosine kinases, using the dual inhibitor BMS-536924, reduced tumor growth in the hyperinsulinemic mice (8). A subsequent study showed that decreasing circulating insulin levels in these mice, using the β_3 adrenergic receptor agonist CL-316243, decreased tumor growth (54). In addition, down-regulating the IR in cancer cells and xenografts reduced cell proliferation, angiogenesis, lymphangiogenesis, and metastasis (55). It was observed that the individuals with GHRD had insulin concentrations that were a third of those in the control population, despite similar glucose levels, which may also contribute to the reduced cancer prevalence in this population (24). *In vitro* studies have demonstrated that colon, breast, prostate, and bladder cancer cells grown in hyperglycemic conditions have accelerated growth upon the addition of insulin (56). This increased growth is associated with an increase in transcription of the genes involved in the regulation of cell cycle progression, such as cyclin A1, cyclin E, and the transcription factor E2F (56). Therefore, it appears plausible that hyperinsulinemia in obese and diabetic individuals may increase the risk of certain cancers by increased IR signaling, leading to proliferative and antiapoptotic effects. And perhaps, reducing insulin levels or blocking insulin signaling in this situation may be sufficient to inhibit tumor growth.

Observational studies have suggested that the insulin sensitizer, metformin, may protect against cancer development. In a group of patients with type 2 diabetes, those taking metformin had a lower risk of developing cancer, compared with those not taking metformin (57). *In vitro* studies on human breast cancer cells demonstrate that metformin up-regulates AMP kinase and inhibits the mammalian target of rapamycin, leading to attenuation of proliferation and cell cycle arrest (58, 59). Whether the affect of metformin on cancer growth is related to its reduction of insulin levels or its intracellular activities on insulin signaling, and the magnitude of its effect in human clinical trials, remains to be determined. Other agents used to treat diabetes, such as insulin secretagogues and insulin therapy, have been reported to increase cancer risk. Whether this is a true effect is as yet uncertain. During the development of modern insulin analogs, analogs were developed that were found to promote tumorigenesis, thought to be due to increased activation of the IGF-IR (60). However, B10Asp, the insulin analog with most mitogenic effects, also had an affinity for the IR twice that of regular human insulin (60). After the epidemiological data emerged in 2009, suggesting that insulin glargine may increase breast cancer risk, further studies were performed to look at the effects of insulin glargine and insulin detemir on the IR and IGF-IR. Stimulation with long-acting insulin analogs produced activation of the IGF-IR, as well as perinuclear accumulation of the IGF-IR. In addition, insulin glargine and insulin detemir displayed antiapoptotic activity, and glargine increased activation of the PI3K pathway (61). To date, these insulin analogs have not been associated with increased cancer risk in randomized trials; therefore, the clinical implications of these observations are uncertain. It is possible that the effect seen is in fact related to differences in endogenous hyperinsulinemia or other confounding factors.

Conclusion

With the increasing prevalence of obesity and type 2 diabetes worldwide, the increased risk of cancer associated with these conditions has received much attention. It appears that the insulin and IGF system play a key role in the pathogenesis of many cancers. Although the initial focus was on the proliferative role of the IGF system in tumor development, after studies using targeted therapy against the IGF-IR, and studies on animal models of hyperinsulinemia, it seems that insulin also has independent effects on tumor growth, and much remains to be discovered in

this field. The words of Charles Best resound today, "Many of the gains made in the field of insulin and diabetes are well consolidated, but a host of new problems, on a much broader front, have appeared" (1).

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