Insulin resistance and cancer: the role of insulin and IGFs

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Abstract

Insulin, IGF1, and IGF2 are the most studied insulin-like peptides (ILPs). These are evolutionary conserved factors well known as key regulators of energy metabolism and growth, with crucial roles in insulin resistance-related metabolic disorders such as obesity, diseases like type 2 diabetes mellitus, as well as associated immune deregulations. A growing body of evidence suggests that insulin and IGF1 receptors mediate their effects on regulating cell proliferation, differentiation, apoptosis, glucose transport, and energy metabolism by signaling downstream through insulin receptor substrate molecules and thus play a pivotal role in cell fate determination. Despite the emerging evidence from epidemiological studies on the possible relationship between insulin resistance and cancer, our understanding on the cellular and molecular mechanisms that might account for this relationship remains incompletely understood. The involvement of IGFs in carcinogenesis is attributed to their role in linking high energy intake, increased cell proliferation, and suppression of apoptosis to cancer risks, which has been proposed as the key mechanism bridging insulin resistance and cancer. The present review summarizes and discusses evidence highlighting recent advances in our understanding on the role of ILPs as the link between insulin resistance and cancer and between immune deregulation and cancer in obesity, as well as those areas where there remains a paucity of data. It is anticipated that issues discussed in this paper will also recover new therapeutic targets that can assist in diagnostic screening and novel approaches to controlling tumor development.

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Introduction

Insulin resistance is a pathological condition characterized by a decrease in efficiency of insulin signaling for blood sugar regulation. Insulin resistance is a major component of metabolic syndrome, i.e. a group of risk factors that generally occur together and increase the risk for various diseases, including type 2 diabetes mellitus and several other metabolic diseases (Campbell 2011, Karagiannis *et al*. 2012), cerebrovascular and coronary artery diseases (Hadaegh *et al*. 2012, Vykoukal & Davies 2012), neurodegenerative disorders (Kaidanovich-Beilin *et al*. 2012,

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Talbot *et al*. 2012), infectious diseases (Jeon *et al*. 2012, Witso 2012), and cancer (Byers & Sedjo 2011, Spyridopoulos *et al*. 2012). Due to the ongoing worldwide epidemic of obesity and other insulin resistance-related disorders (Campbell 2011), insulin-like peptides (ILPs), i.e. evolutionary conserved and ubiquitous factors historically involved in the regulation of energy metabolism, have been the subject of thorough investigations. In humans, ILPs include insulin, IGF1, IGF2, and seven relaxin-related peptides, which share the same basic fold (Sajid *et al*. 2011). In the present review, the term 'ILP' will be used to indicate insulin and IGFs, whereas relaxin-related peptides will not be discussed.

Insulin signal transduction occurs through two insulin receptor (IR) isoforms resulting from transcriptional alternative splicing: the 'A' isoform (IR-A) that recognizes insulin and IGFs, with a greater affinity for IGF2 than IGF1, and the IR 'B' isoform (IR-B), which is insulin specific and mainly involved in glucose homeostasis (Zhang & Roth 1991, Artim *et al*. 2012). In healthy individuals, blood glucose concentrations are maintained within narrow physiological range by a state of balance between insulin production by specialized pancreatic β-cells and insulin-mediated glucose uptake in target tissues, which is further determined by the translocation of glucose transporters, of which GLUT-4 is the most abundant, to the cell surface (Kern *et al*. 1990). Evidence that insulin resistance in classic insulin-target organs, together with the associated hyperglycemia and hyperinsulinemia (followed by hypoinsulinemia) are the pathological hallmark of metabolic disorders such as obesity and type 2 diabetes is compelling (Ricketts 1947, Berry & Helwig 1948, Ahmed *et al*. 2012, Aldhafiri *et al*. 2012). Several population-based studies revealed a decrease in cancer risk in diabetic patients assuming antidiabetic agents of the biguanide family such as metformin (Pezzino *et al*. 1982, Suissa 2008, Kiri & Mackenzie 2009). On the other hand, a growing body of evidence indicates an association between type 2 diabetes and an increase in risk of developing breast, prostate, colon, endometrial, and ovarian cancers (Alvino *et al*. 2011, Tan *et al*. 2011, Tzivion *et al*. 2011, Mu *et al*. 2012).

Data obtained from independent studies involving *Drosophila* model show that ILPs have specialized functions including regulating cell proliferation, differentiation, survival, and apoptosis, thus playing a pivotal role in cell fate determination and life span control (Bai *et al*. 2012, Bolukbasi *et al*. 2012). Such functions are evolutionarily conserved (Duckworth *et al*. 1989, Klusza & Deng 2011), and accordingly, the stimulation of IGF1 axis may represent a common medium for both cancer and diabetes pathogenic processes, together with systemic inflammation and the associated increase in cytokine production (Nunez *et al*. 2006, Dool *et al*. 2011, Faria & Almeida 2012, Ferguson *et al*. 2012, Fernandez-Real & Pickup 2012, Gallagher *et al*. 2012). Except for the IGF2 receptor (IGF2R), following ligand binding, the kinase activity of ILP receptors is activated, leading to the phosphorylation of IR substrates in the cell membrane, which in turn i) activates phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), PI3K/Akt/forkhead box O (FoxO), and Ras/MAPK/extracellular signal-related kinase 1/2 (ERK-1/2) pathways, whose important roles in cancer cell growth and carcinogenesis have been reported (Alvino *et al*. 2011, Tzivion *et al*. 2011); and ii) inactivates glycogen synthase kinase 3β (GSK3β), the inhibitor of the oncogenic β-catenin signaling, through PI3K/Akt signaling pathway, resulting in β-catenin signaling activation that has been associated with cancer stemness and chemoresistance (Fleming *et al*. 2008, Ashihara *et al*. 2009; see Fig. 1). Other ILP receptors include the IGF1 receptor (IGF1R) that recognizes both IGF1 and IGF2; holoreceptors made up of combinations of half IGF1R and IR isoforms or other tyrosine kinases; and finally the IGF2R that recognizes only IGF2 (Rinderknecht & Humbel 1978) and attenuates IGF2 signaling by clearing the ligand from cell surface without signal transduction (Artim *et al*. 2012). IGFs also bind to carrier proteins named 'IGF-binding proteins' (IGFBP).

Contrary to insulin, IGFs are produced by many cell types, although the liver is their main site of production. IGF1 production in the liver is stimulated by GH (Blethen *et al*. 1981, Madsen *et al*. 1983). IGFs have characteristics of both hormones and tissue growth factors, and consequently, they can induce both local and systemic responses (Blundell *et al*. 1978, Sajid *et al*. 2011). Tissues that classically respond to IGFs preferentially express the IGF1R, and nonclassic target tissues including cancer cells express both the latter receptor and IR-A genes and may display hybrid receptors as well, which probably account in carcinogenesis and chemoresistance (Artim *et al*. 2012, Pierre-Eugene *et al*. 2012).

In the present review, we critically summarize recent reports indicating a crucial role of insulin, IGFs, and their receptors in cancer development and maintenance. A unifying model for the high cancer risks and chemoresistance associated with insulin resistance, in obesity and type 2 diabetes cases, will also be discussed.

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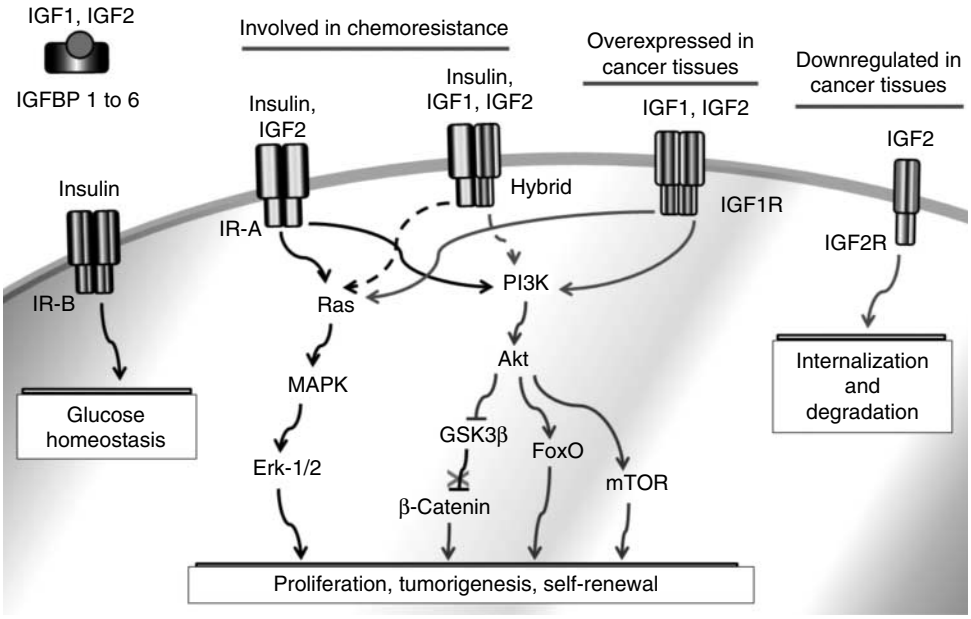

Figure 1

ILP signaling and cancer. ILP receptors are structurally related tyrosine kinase receptors. Canonical insulin receptor isoform 'A' (IR-A), isoform 'B' (IR-B), IGF1 receptor (IGF1R), and hybrid receptor (holoreceptors made of combinations of half IGF1R and IR isoforms or other tyrosine kinases) signaling are mediated through downstream pathways like phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), PI3K/Akt/forkhead box O (FoxO), Ras/MAPK/extracellular signal-related kinase 1/2 (ERK-1/2) pathways, or through PI3K/Akt-mediated inactivation of glycogen synthase kinase 3β (GSK3β) that results in the accumulation of β-catenin and in the activation of its downstream targets. The IGF2 receptor (IGF2R) attenuates IGF2 signaling by clearing that molecule from the cell surface without signal transduction. Overexpression of IGF1R signaling and downregulation of IGF2R are commonly reported in cancer, as well as the overexpression of IR-A and hybrid receptor signaling in the presence of abnormally high levels of insulin and IGFs.

ILPs, insulin resistance, and cancer risk

ILP molecules and cancer risk

Data sustaining an association between IGF1 and cancer risk include recent studies from Mora *et al*. (2011) in elderly, which have suggested that genetic variations in the insulin/IGF1 pathway genes are associated with longevity, dementia, metabolic diseases, and cancer. However, ILP association with cancer risk is still debated, as controversial data have been reported. In a study assessing the link between overall cancer mortality and circulating IGF1 or IGFBP3 levels, no significant association was found (Kaplan *et al*. 2012). However, another recent clinical study has indicated that IGF1 is positively associated and IGFBP3 is inversely associated with all-cause mortality in men with advanced prostate cancer (Rowlands *et al*. 2012), indicating that levels of IGF1 and IGFBP3 may have potential as prognostic markers in predicting risk of death in men with advanced prostate cancer. A comparable study has revealed a correlation between zinc, IGF1, and IGFBP3 concentrations, and prostate-specific antigen in prostate cancer, and findings have indicated that zinc, IGF1, and IGFBP3 can be useful in early diagnosis of prostate cancer (Darago *et al*. 2011). In addition, other investigators reported that *IGFBP3* gene polymorphism would be associated with the susceptibility to develop prostate cancer (Safarinejad *et al*. 2011*a*). A report from Price *et al*. (2012) indicates that increases in circulating IGF1 levels are associated with a significantly increased risk for prostate cancer development. Interestingly, this positive association did not differ depending on the duration of follow-up for cancers diagnosed more than 7 years after blood collection, or by stage, grade, and age at diagnosis or age at blood collection, and raise up the question whether reducing circulating IGF1 levels may affect prostate cancer risk. Moreover, IGF1 serum levels are increased in patients with locally advanced colorectal cancer (pT3 and pT4), in comparison to less advanced (pT2); a higher serum level of IGF1 is observed in patients with poorly differentiated cancers (G3) than in moderately differentiated, and similarly, higher serum levels of IGF1 are found in male

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patients older than 60 years and in mucigenous colorectal cancers (Kuklinski *et al*. 2011). The risk of colorectal cancer would also be associated with higher IGF1/IGFBP3 ratio or C-peptide levels (Wu *et al*. 2011).

A possible explanation for the differences between the observations of the first investigators and the following ones has been provided by studies of Henningson *et al*. (2011) and Masago *et al*. (2011). Both studies reported experimental and clinical data suggesting a correlation between interpersonal variability in IGF1 levels and cancer risk. These findings indicate that according to the type of cancer considered and at an individual basis, the importance of ILP molecules for cancer risk evaluation can change. Another illustration can be provided by recent studies in colorectal adenoma. In a first clinical study, only the increases in circulating IGF1 and IGF1/IGFBP3 ratio have been reported to represent a disturbed GH/IGF1 homeostasis, which could favor the development of precancerous lesions such as colorectal adenoma, and to be, therefore, an indicator of the risk of cancer development (Soubry *et al*. 2012), suggesting that IGF1 is associated with the pivotal precursor to colorectal cancer. On the other hand, in another clinical study, although a positive association between circulating IGF1 levels and the risk of advanced colorectal adenoma was observed as well, IGFBP3 levels and IGF1/IGFBP3 ratio were not indicative of cancer risk, whereas elevated IGF2 levels were indicative instead (Gao *et al*. 2012). Considering that most studies evaluating the link between ILP molecules and cancer risk have been performed on small cohorts, large prospective studies are required to better characterize the potential roles of ILP molecules for cancer risk evaluation and reduce the bias created by interindividual variability. Interestingly, findings from a population-based study, where components of the IGF axis did not appear to be risk factors for pancreatic cancer, have indicated that it cannot be excluded that a relatively large amount of IGF1 together with very low levels of IGFBP3 might still be associated with an increase in cancer risk (Rohrmann *et al*. 2012), given that statistical subanalysis may not reflect the physiopathological reality. Data from a study adopting such approach have indicated that high-grade prostate cancers would be more autonomous and, thus, less sensitive to the action of IGF1 than low-grade cancers (Nimptsch *et al*. 2011), explaining discrepancies in the findings between different studies and the lack of statistical significance reported by many investigators. Further studies should consider better experimental design to reduce biases in statistical subanalysis and should be designed to analyze the data mainly on the basis of their clinical value and less so on their mathematical/statistical significance.

Similar findings have been reported in other types of cancers. IGF1 and IGF1/IGFBP3 molar ratio might increase mammographic density and thus the risk of developing breast cancer (Campagnoli *et al*. 1992, Byrne *et al*. 2000). In familial breast cancer, an association between IGF1 levels and cancer development has been reported (Rosen *et al*. 1991, Bruning *et al*. 1995, Pasanisi *et al*. 2011), and IGF1 may predict higher risk of recurrence in breast cancer survivors (Al-Delaimy *et al*. 2011). Associations of IGF1 and IGF1/IGFBP3 ratio with mortality in women with breast cancer have also been reported (Duggan *et al*. 2012, Izzo *et al*. 2012). However, all these data need to be confirmed in larger breast cancer survivor cohorts, considering that other reports have indicated that serum concentrations of IGF1 and IGFBP3 do not correlate with breast cancer development/risk (Trinconi *et al*. 2011).

Other controversies have been reported. Although most investigators have reported a positive association between IGF1 level (or IGF1/IGFBP3 ratio) and cancer risk, others have reported significant inverse associations, including in prostate cancer (Alokail *et al*. 2011) and melanoma (Panasiti *et al*. 2011, Park *et al*. 2011*b*), for example. In addition, whereas large increases in IGFBP1 were reported to significantly raise the risk of overall cancer mortality in patients (Kaplan *et al*. 2012), global Igfbp1 deletion does not affect prostate cancer development in a *c-Myc* transgenic mouse model (Gray *et al*. 2011). These observations emphasize the need for large cohort studies.

Energy balance, insulin resistance, and cancer risk

Although many independent reports have suggested the existence of a link between energy imbalance and cancer in insulin resistance-associated metabolic disorders, data demonstrating such a direct mechanistic link are lacking. Interestingly, it has been reported that long-term low-protein, low-calorie diet and endurance exercise, which lowers insulin levels, modulate metabolic factors associated with cancer risk (Fontana *et al*. 2006). More recent studies have revealed that diets leading to weight gain and hyperinsulinemia increase the expression of IR-A on cancer cells (Algire *et al*. 2011), indicating that insulin level changes can mediate the effects of energy balance in cancer. A recent meta-analysis assessed the correlation between intentional weight loss and cancer risk reduction (Byers & Sedjo 2011). The investigators analyzed all available literature reporting changes in cancer risk

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following intentional weight loss, as well as reports addressing changes in major cancer risk factors, including IGFs and IGFBPs, estrogens, and sex hormone binding globulin (SHBG), as well as inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin 6 (IL6). Interestingly, the findings from this study suggest that cancer incidence was reduced after intentional weight loss in about all observational cohort studies and randomized controlled trials of both dietary interventions and bariatric surgery. In addition, a correlation was observed between intentional weight loss and decrease in estrogen level as well as SHBG level increase with up to threefold reduction in free estradiol from a 10% weight loss. The weight loss was accompanied by a decrease in pro-inflammatory factor expression, notably, with a comparable 3:1 ratio in CRP levels drop. The reductions in circulating TNF-α and IL6 were consistent as well, although at smaller magnitude. Surprisingly, IGF1 and IGFBP changes observed after weight loss were inconsistent. Collectively, these observations suggest that estrogen and circulating pro-inflammatory factors are the major players in cancer risk decrease caused by body weight loss, unlike IGF1. It has been hypothesized that abnormally high levels of growth factors, adipokines, reactive oxygen species, adhesion factors, and pro-inflammatory cytokines observed under conditions of insulin resistance create a favorable niche for neoplastic tissue survival and cancer stem cell development, with tumors behaving like 'wounds that never heal' to ensure their maintenance (Sakurai & Kudo 2011, Pollak 2012, Seke Etet *et al*. 2012). Considering that in most cases both cancer incidence and levels of circulating cancer biomarkers drop relatively rapidly following intentional weight loss (Byers & Sedjo 2011), the latter should be further investigated as a meaningful approach for cancer risk reduction.

Although there are controversial data, recent findings, mostly from population-based studies, have pointed out a link between glucose metabolism, insulin levels, and cancer risk. For instance, an epidemiological study evaluating pancreatic cancer risk factors has revealed that type 2 diabetes is the third major risk factor for this disease (Li 2012). A recent meta-analysis of observational studies has revealed that insulin resistance is a significant risk factor for endometrial cancer, particularly when associated with high levels of circulating adipokines like adiponectin, leptin, and plasminogen activator inhibitor-1, as well as androgens and inflammatory mediators (Mu *et al*. 2012). It is widely accepted that diabetic patients have relatively increased cancer risk as well as worse cancer prognosis, in comparison with individuals without diabetes. However, a recent study involving 25 476 patients with type 2 diabetes has not found any association between HbA1c and risks for all cancers or specific types of cancer (Miao Jonasson *et al*. 2012). Instead, experimental data indicate the overexpression of ILP observed in these patients as a cancer risk factor (Ferguson *et al*. 2012, Gallagher *et al*. 2012). The hyperinsulinemia resulting from the body's attempt to compensate insulin resistance in type 2 diabetes may benefit fully insulin-sensitive cancer tissue by substantially increasing their growth through IR-A/IGF1R increased signaling. However, whether type 2 diabetes leads to increased IR-A/IGF1R signaling in neoplastic cells in comparison with normal insulin target tissues is still controversial and requires further studies. Whereas some reports indicate that tumors respond favorably to ILP overexpression (Nagamani & Stuart 1998, Ferguson *et al*. 2012, Gallagher *et al*. 2012), other reports indicate that hyperinsulinemia is associated with only a modest increase in tumor growth rate (Kalme *et al*. 2003, Algire *et al*. 2011, Pollak 2012). Further studies investigating ILP signaling role in cancer tissues may provide better understanding of cancer biology and reveal novel therapeutic targets.

ILP molecules and carcinogenesis

Various striking observations and findings indicating a link between ILP molecules and cancer are summarized in Table 1.

Insulin

Studies evaluating insulin secretion, as reflected by C-peptide levels, have pointed out a correlation between high plasma concentration of insulin and poor clinical outcome and death in prostate cancer (Ma *et al*. 2008). A recent study has shown that aldo-keto reductase 1B10 (AKR1B10), which plays a critical role in tumor development and progression through promoting lipogenesis and eliminating cytotoxic carbonyls, is induced by mitogen epidermal growth factor (EGF) and insulin through the activator protein-1 (AP-1) signaling pathway in human hepatocellular carcinoma cells (Liu *et al*. 2012). Most recent reports have also suggested that insulin has mitogenic and anti-apoptotic effects in endometrial cancer, and the activation of IR-A, IR substrate 1, and Akt is associated with aggressive features (Wang *et al*. 2012). Proinsulin, the prohormone precursor to insulin characterized by low metabolic activity, binds with high

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Table 1 Recent striking observations indicating a link between ILPs and cancer risk.

	Observations
Insulin	Association of mutations in insulin/IGF1 pathway genes with cancer (Mora *et al*. 2011)
IR-A	IR-A upregulation on cancer cells (Algire *et al*. 2011)
	IR-A activation associated with aggressive features in endometrial cancer (Wang *et al*. 2012)
IGF1	IGF1 promotes prostate cancer growth (Rabiau *et al*. 2011, Takahara *et al*. 2011)
	High IGF1 levels associated with increased risk for prostate cancer (Alokail *et al*. 2011, Price *et al*. 2012), melanoma (Park *et al*. 2011*b*), colorectal cancer (Kuklinski *et al*. 2011, Gao *et al*. 2012), and breast cancer (Al-Delaimy *et al*. 2011)
IGF1R	IGF1R universal expression in multiple myeloma cells (Barbosa *et al*. 2011)
IGF1/IGFBP3 ratio	High IGF1/IGFBP3 ratio associated with increased risk for colorectal cancer (Wu *et al*. 2011) and melanoma (Panasiti *et al*. 2011)
	Prognostic marker of death in prostate cancer (Darago *et al*. 2011, Rowlands *et al*. 2012) and breast cancer (Duggan *et al*. 2012, Izzo *et al*. 2012, Meggiorini *et al*. 2012)
IGFBPs	*IGFBP3* gene polymorphism association with risk for prostate cancer (Safarinejad *et al*. 2011*a*) and bladder cancer (Safarinejad *et al*. 2011*b*)
	High IGFBP1 levels associated with overall cancer mortality (Kaplan *et al*. 2012)
	IGFBP5 and IGFBP7 levels predict lung cancer (NSCLC) outcome (Shersher *et al*. 2011)
IGF2	IGF2 prognostic molecular biomarker in hepatocellular carcinoma (HCC) (El Tayebi *et al*. 2011), prostate cancer (Rowlands *et al*. 2012), and intrathoracic tumors (Thabit *et al*. 2011)
IGF2R	IGF2 mutations associated with risk for oral cancer (Yoon *et al*. 2012), colon cancer (Hoyo *et al*. 2012), and hepatocellular carcinoma (Couvert *et al*. 2012)

HCC, hepatitis C-related cirrhosis; IGF1R, IGF1 receptor; IGF2R, IGF2 receptor; IGFBP, IGF-binding protein; IRs, insulin receptors; NSCLC, non-small cell lung cancer.

affinity to IR-A and predominantly activates the ERK/p70S6K mitogenic pathway to a similar degree as insulin; in addition, proinsulin was almost equipotent as insulin in inducing cell proliferation and migration in three human cancer cell lines expressing various IR-A levels (Malaguarnera *et al*. 2012). IR-A and IGF1R are homologous to tyrosine kinase class oncogenes and share about 60% homology (Rowzee *et al*. 2009). IR-A is commonly expressed by tumors, and most cancer cells express *IGF1R* gene, but activating mutations of these receptors are rare (Avnet *et al*. 2009, Kim *et al*. 2012), indicating that ligand-mediated triggering of ILP signaling is mandatory for ILP carcinogenic effect. Unlike IGFs, local production of insulin by tumors is uncommon (Venkateswaran *et al*. 2007, Klement & Kammerer 2011). However, a recent study investigating the range of autoinhibitory mechanisms used by tyrosine kinase domains (TKDs) from the IR family has revealed a wide range of expected activating mutations in cancer (Artim *et al*. 2012).

IGF1

Experimental data suggest that IGF1 plays a role in carcinogenesis. For instance, clinical and experimental studies have revealed that *IGF1* gene is specifically expressed in tumor tissues in prostate cancer (Koutsilieris *et al*. 1993, Culig *et al*. 1994, Rabiau *et al*. 2011). A study performed in lit/lit mice transplanted human prostate cancer xenografts has demonstrated that circulating GH and IGF1 promote androgen-responsive growth, castration-resistant progression, and androgen-independent expansion of human prostate cancer cell xenografts (Takahara *et al*. 2011). Interestingly, IGF1 successfully promoted prostate cancer growth in a suppressed GH environment. In lung and breast cancers, an association between the marked expression of phosphorylated/activated IGF1Rs and poor clinical outcome has been reported (Law *et al*. 2008, Furukawa *et al*. 2010, Kim *et al*. 2012). Recent data have also suggested IGF1 involvement in the pathogenesis of various blood cancers. For instance, in multiple myeloma, IGF1R has been reported as one of the major mediators of growth and survival of cancer cells (Jernberg-Wiklund & Nilsson 2012). In a mouse model of acute myelogenous leukemia, IGF signaling has been reported to contribute to the malignant transformation of hematopoietic progenitors via a mechanism involving the receptor tyrosine kinase FLT3 (Stubbs *et al*. 2008) and the fusion oncoprotein MLL-AF9 (Jenkins *et al*. 2012). IGF1R is universally expressed in multiple myeloma cells (Freund *et al*. 1994, Barbosa *et al*. 2011), and insulin and IGFs are potent myeloma cell growth factors through insulin/IGF1 hybrid receptor activation (Freund *et al*. 1993, Sprynski *et al*. 2010). Moreover, a recent study addressing the effect of five marketed insulin analogs on insulin/IGF1 hybrid receptors have indicated that

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IR-A/IGF1 hybrid receptors are present in most tissues and mediate biological effects close to those of IGF1R (Pierre-Eugene *et al*. 2012). The study revealed that the insulin analog glargine displays higher proliferative and anti-apoptotic effects than insulin in the breast cancer cell line MCF-7, probably through IR-A/IGF1R hybrids.

IGF2

Recent evidence indicates that IGF2R plays a crucial role in cancer prevention attributed to its antagonist role on cellular growth and evidence of loss of heterozygosity in several cancers including breast cancer (Cheng *et al*. 2009). Loss of function mutations in the gene encoding for this receptor were reported in various cancers, including hepatocellular carcinoma (De Souza *et al*. 1995); breast carcinoma (Chappell *et al*. 1997); endometrial, gastric, and colorectal cancers (Ouyang *et al*. 1997); squamous cell carcinoma (Probst *et al*. 2009); and ovarian cancer (Kuhlmann *et al*. 2011). RNA interference with the expression of the bioactive complex mannose-6-phosphate (M6P)/IGF2R in urokinase-type plasminogen activator (uPA) or uPA receptor (uPAR) expressing human cancer and endothelial cells results in increased pericellular plasminogen activation, cell adhesion, and higher invasive potential, and M6P/IGF2R silencing also leads to the cell surface accumulation of urokinase and plasminogen, as well as an enhanced expression of alpha V integrin (Schiller *et al*. 2009), indicating that M6P/IGF2R controls cell invasion by regulating alpha V integrin expression and by accelerating uPAR cleavage. Besides, plasminogen activation cascade plays a central role in cell migration and in angiogenesis (Pepper *et al*. 1987, Takano *et al*. 1994). Leksa *et al*. (2012) reported that M6P/IGF2R can control cancer cell migration and impede aberrant angiogenesis (Leksa *et al*. 2011) by blocking plasminogen activation and modulating its uptake by transforming cells. Furthermore, Probst *et al*. (2009) have shown that M6P/IGF2R-deficient SCC-VII murine squamous cell carcinoma cells secrete large amounts of pro-invasive lysosomal proteinases, with an impairment of the formation of mature lysosomes. Interestingly, M6P/IGF2R expression reduced the invasive capacity of SCC-VII cells in response to various chemoattractants, indicating that the M6P/IGF2R status influences the metastatic propensity of squamous cell carcinomas. Besides, loss of heterozygosity proximal to the M6P/IGF2R locus is predictive for the presence of disseminated tumor cells in the bone marrow of ovarian cancer patients (Kuhlmann *et al*. 2011), and M6P/IGF2R restricts liver cell invasion by preventing the pericellular action of M6P-modified proteins in tumorigenic rodent liver cells (Puxbaum *et al*. 2012). A recent report has elegantly demonstrated that M6P/IGF2R truncation mutants may in fact contribute to the cancer phenotype by decreasing the availability of full-length M6P/IGF2Rs to perform tumor-suppressive functions including internalization of receptor ligands such as IGF2 (Kreiling *et al*. 2012).

Moreover, overexpressed IGF2 can mediate carcinogenic effects through IR-A (Wang *et al*. 2012). Notably, IGFs originate from both local and systemic productions in cancer (Fagin *et al*. 1988, Foulstone *et al*. 2003) and are commonly expressed by cancer cells (Venkateswaran *et al*. 2007, Klement & Kammerer 2011). Morcavallo *et al*. (2011) performed quantitative proteomics of insulin-A substrates recruited to tyrosine-phosphorylated protein complexes following either insulin or IGF2. Of the 38 substrates identified, 28 substrates had not been previously related to IR-A signaling pathway, and ten were well known ones. Interestingly, whereas 11 substrates were recruited by both ligands, 14 were recruited solely by IGF2 and 13 by insulin alone. Discoidin domain receptors, which are involved in cell migration and tumor metastasis, and ephrin receptor B4, which is involved in cell migration, were predominantly activated by IGF2. In addition, more recent studies performed by the same investigators (Morcavallo *et al*. 2012) have revealed that insulin and IGF2 also affect IR-A biological responses by differentially regulating the receptor trafficking. For instance, whereas a downregulation of IR substrate 1 was observed after prolonged insulin exposure, no comparable effect was observed with IGF2. Conversely, insulin induced significant receptor internalization following signal transduction whereas IGF2 induced only a modest internalization. Overall, the study observations suggested that the lower affinity of IGF2 for the receptor, which causes a less powerful activation of early downstream effectors in comparison with insulin, also protects the receptor and its substrates from downregulation, thereby resulting in sustained mitogenic stimuli.

Insulin resistance, immune response alterations, and cancer: ILP involvement

Immune response alterations and carcinogenesis

ILP molecules have been reported to play a crucial role in altered inflammatory responses to infectious challenge commonly observed in insulin resistance-related metabolic disorders (Fenton *et al*. 2009, Bitar & Al-Mulla 2012).

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Some of the commonly reported alterations in obesity and type 2 diabetes include deregulated lymphopoiesis and lymphocyte proliferation, altered antigen presentation, and altered pathogen recognition (Mandel & Mahmoud 1978, Chandra 1981), which are caused at least in part by an aberrant adipocyte–leukocyte cross talk (Stienstra *et al*. 2011). Experimental evidence suggests that the abnormally high number of inflammatory cells in adipose tissue of obese subjects and type 2 diabetes patients may promote systemic inflammation and a microenvironment favorable for neoplastic cell survival and proliferation. For instance, aberrant alveolar macrophages contribute to worsening lung infection and autoimmunity in type 2 diabetes patients (Sunahara & Martins 2012). Fritz *et al*. (2011) have recently demonstrated that alveolar macrophages release IGF1, which stimulates neoplastic mouse lung cell proliferation through PI3K/Akt and MAPK/ERK activation. Interestingly, their findings also indicate that combining macrophage ablation therapy with IGF1R, MEK, and/or PI3K inhibition may improve therapeutic response in human lung cancer. On the basis of comparable findings, it has been hypothesized that high levels of circulating inflammatory factors and ILPs cause adipocyte activation, resulting in the release of pro-inflammatory adipokines, free fatty acids, and chemoattractant factors that attract and trap circulating macrophages into fat tissue; then, infiltrating macrophages would amplify the adipocyte signals, resulting in immune response deregulation (Glass & Olefsky 2012). Experimental data sustaining this theory also include early reports indicating an improvement of immune response following gastric bypass and weight loss (Grace *et al*. 1986, Tanaka *et al*. 1993), and recent reports indicating that a high-fat diet increases aberrant angiogenesis, solid tumor growth, and lung metastasis of CT26 colon cancer cells, even in obesity-resistant BALB/c mice (Park *et al*. 2011*a*), and comparable studies indicating that decreased systemic IGF1 in response to calorie restriction modulates murine tumor cell growth, NF-κB activation, and inflammation-related gene expression (Harvey *et al*. 2012). In addition, adipocyte-released IGF1 is regulated by glucose and fatty acids and controls breast cancer cell growth *in vitro* (D'Esposito *et al*. 2012).

Moreover, the activation of the IGF1R and IR-A signaling target mTOR accounts for at least part of the enhancing effects of obesity on mammary tumor growth (Gallagher *et al*. 2012), and such effects are reversed by the mTOR inhibitor RAD001 in mouse models of obesity (De Angel *et al*. 2012). Besides, macrophages express leptin receptors, which play a crucial role in the innate immune response, particularly through activation of JAK–STAT signaling pathway, which is the canonical cytokine receptor signaling pathway, and through activation of ILP signaling downstream targets like PI3K/Akt/m-TOR/p70S6K and MAPK/ERKs pathways (Lee *et al*. 1999, Algire *et al*. 2011). Leptin triggers the production of pro-inflammatory factors, such as TNF-α, IL1, IL6, and leukotriene B4 that normally result in the increase of immune cell survival, maturation, and proliferation. However, the drastically increased levels of circulating leptin characteristic of obesity and type 2 diabetes may cause cell adherence and pathogen recognition impairments instead and probably contribute to the occurrence of abnormally increased levels of pro-inflammatory factors in these pathological conditions (Ropelle *et al*. 2010). Other recent studies have shown alterations in rolling, adhesion, and migration of leukocytes to the site of infection in diabetic mice (Spiller *et al*. 2012).

Notably, insulin resistance treatment improves some indices of immune response both in experimental models and in patients. Recent clinical studies involving patients with morbid obesity and type 2 diabetes mellitus have revealed a reduction in endotoxemia, oxidative stress, systemic inflammation, as well as insulin resistance following gastric bypass surgery (Monte *et al*. 2012). Recent findings in monocytes from obese subjects, where insulin resistance is associated with increases in oxidative stress and activation of pro-inflammatory signaling molecules like c-Jun NH (2)-terminal kinase (JNK) and nuclear factor κB inhibitor kinase (IKK-β), indicate that the induction of stress kinase inhibitors such as heat-shock proteins (Hsp) 72 and Hsp27 improves insulin signaling via inhibition of stress kinases and the reduction of serine phosphorylated/inactivated IR substrate 1 (Simar *et al*. 2012). Studies in obese mice have shown that targeting inflammatory dendritic cells improves insulin response resistance through NF-κB (Yekollu *et al*. 2011). However, despite these promising observations, whether insulin resistance treatment or direct pharmacological targeting of inflammation suffices to completely restore the immune response in obese subjects and diabetic patients is still controversial. Some recent clinical studies have reported insulin resistance treatment failure to restore the immune response in several cases (Fernandez-Real & Pickup 2012, Karagiannis *et al*. 2012), indicating that mechanisms accounting for immune deregulation in insulin resistance-related metabolic disorders are complex and require further studies.

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Insulin resistance, infection, and cancer

In the last decades, a substantial body of evidence from humans and animal models has indicated a link between insulin resistance and impaired immune response to infectious challenges. The deregulation of pathogen recognition in insulin resistance-associated conditions and diseases (Lee *et al*. 1999) induce the body to trigger a sustained inflammatory response against mutualistic microorganism of the intestinal gut, such as the stomach common bacterium *Helicobacter pylori* (Grote *et al*. 2012, Wang *et al*. 2012). An increasing body of evidence from epidemiological studies has suggested an association between diabetes mellitus and *H. pylori* infection (Jeon *et al*. 2012). These data further suggest that beyond the high-fat diet hypothesis (Oldham 2011), this micro-organism may account as a causative agent for the ongoing diabetes mellitus pandemic (Campbell 2011). In addition, *H. pylori* infection has also been implicated in carcinogenesis; however, the actual mechanism on how the bacterium causes cancer is still controversial. For instance, *H. pylori* has been reported to confer protective effects against esophageal cancer (Islami & Kamangar 2008), but on the other hand, together with hepatitis B and C viruses, and human papillomaviruses, the bacterium is responsible for about a third of all cancers attributable to infections, mainly including gastric, liver, and cervix uteri cancers (de Martel *et al*. 2012, Sakitani *et al*. 2012). In addition, silent infection with *H. pylori* is a source of pro-inflammatory cytokines and IGF1 in hyperinsulinemia conditions (Aguilera *et al*. 2004, Ozen *et al*. 2011). Unraveling the precise role of ILP molecules in *H. pylori*-related carcinogenesis may provide novel pharmacological targets for micro-organism-related cancers.

Hepatitis C virus has also been reported to cause permanent liver damage and hepatocellular carcinoma (Amitrano *et al*. 1990, Farinati *et al*. 1992), at least in part through oxidative stress, inflammatory response, and insulin resistance-related mechanisms (Nishida & Goel 2011, de Martel *et al*. 2012, Oliveira *et al*. 2012). Interestingly, a recent clinical study has provided evidence for metabolic syndrome in nonobese and nondiabetic patients with chronic hepatitis C virus genotype 1 infection; this metabolic syndrome was associated with overweight, increased abdominal fat, hypertension, and insulin resistance (Oliveira *et al*. 2012). Early clinical studies and studies from animal models suggested an association of hepatitis C virus with insulin resistance, and in a more recent study, an association of the virus nonstructural protein 5A (NS5A) with insulin resistance has been reported (Badar *et al*. 2012). Furthermore, positive changes in adipokine levels and insulin sensitivity have been observed following antiviral therapy targeting hepatitis C genotype 4 (Khattab *et al*. 2012), suggesting a direct role of the virus in the insulin resistance that accompany the infection. Interestingly, an *in vitro* study has shown that hepatitis C virus can induce insulin resistance by inhibiting IR substrate 1 function, i.e. ILP receptor metabolic activity, and through activation of the mTOR/S6K1 signaling pathway (Bose *et al*. 2012). Another study has revealed a significant proteasomal degradation of IR substrate 1 protein triggered by NS5A in a dose-dependent way (Alberstein *et al*. 2012). In addition, depletion in levels of circulating IGF1 has been observed in this viral infection (Helaly *et al*. 2011). Altogether, these observations point out hepatitis C virus as a causative agent of insulin resistance. Furthermore, given the previously discussed ability of insulin resistance to decrease metabolic and increase pro-carcinogenic effects of ILP signaling, insulin resistance may play a crucial role in the chemoresistance observed in hepatitis C-related hepatocarcinoma, and therefore, anti-ILP strategies may prove efficient against this disease.

ILP signaling, insulin resistance, and cancer treatment

ILP targeting as anticancer strategy

ILP signaling via the PI3K/Akt/mTOR pathway is a potential therapeutic target for many cancer types, including breast and prostate cancers (Alvino *et al*. 2011, Tzivion *et al*. 2011). Many drug candidates targeting ILPs have entered clinical trials, and ILP targeting appears to be a promising anticancer strategy. Clinical trials evaluating the drugs targeting ILPs have been recently reviewed (Pollak 2012, Tognon & Sorensen 2012). Antibodies specifically targeting IGF1R are already in phase III trials, whereas other classes are in less advanced phases (Gualberto & Pollak 2009, Kalra *et al*. 2012). In addition, a phase II study addressing the efficiency of IGF1 antibody figitumumab in non-small-cell lung cancer patients have shown that only patients with abnormally high levels of IGF1 and low levels of IGFBP1 can have a substantial improvement following treatment (Gualberto *et al*. 2011), indicating that IGF1/IGFBP1 ratio can be predictive of figitumumab clinical benefit. Cixutumumab (IMC-A12), another MAB specifically targeting IGF1R, is relatively safe and enhances the tumor growth inhibitory and

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pro-apoptotic effects of several chemotherapeutics (Rowinsky *et al*. 2011, Kalra *et al*. 2012). However, hyperglycemia and hyperinsulinemia have been reported in some patients, together with increases in GH secretion (Gualberto & Pollak 2009), indicating pituitary gland attempts to compensate for the lack of IGF1 signaling feedback. Compensatory increases in IR-A following IGF1R silencing and altered insulin B expression resulting respectively in chemoresistance and perturbations in glucose homeostasis were reported as well.

Besides, small-molecule tyrosine kinase inhibitors aiming at targeting IGF1R activity have also been developed. Tremendous undesired effects, and in particular severe metabolic toxicity similar to diabetes mellitus complications, were expected from these molecules that tend to inhibit all ILP activity. Instead, evidence from early clinical experience indicates that these agents are safe and, therefore, promising, given their broader range of receptor inhibition (Chan *et al*. 2011, Zhou *et al*. 2011). The mechanisms explaining the absence of the expected side effects still are to be unraveled, even though some plausible explanations have been suggested. For instance, the low penetration of major sites of insulin-stimulated glucose disposition such as the muscle and the incomplete inhibition of ILP receptor signaling have been hypothesized (Dool *et al*. 2011).

The downstream targets of the canonical ILP signaling include the survival pathway PI3K/Akt that can activate downstream targets like mTOR and FoxO/BAD/Bcl-2 but also inhibit GSK3β, resulting in the activation of the oncogenic β-catenin signaling pathway (Fleming *et al*. 2008, Ashihara *et al*. 2009). In the last decade, PI3K, Akt, mTOR, FoxO, BAD, Bcl-2, β-catenin, and other signaling molecules involved in cell survival and proliferation have been the subjects of investigation of many studies aiming at unraveling carcinogenic mechanisms. These pathways are targets of most tyrosine kinase receptors, indicating that successful targeting would be potentially effective not only against ILP-related cancers but also against aberrant activations of other major anti-apoptotic signaling networks initiated by non-ILP receptor tyrosine kinases. Anticancer effects of β-catenin targeting are well known in many cancer types, and anticancer drugs targeting this pathway were developed and include cyclopamine for instance. Similarly, BAD/Bcl-2 pathway is the target of the signaling pathways of many oncogenes, including Notch. Notch signaling blockade is used as anticancer therapy, and effective drugs such as γ-secretase inhibitors were developed for various cancers (Margheri *et al*. 2012, Seke Etet *et al*. 2012). Thus, the ILP signaling inhibition may mediate its anticancer effects, at least in part, by modulating these signaling pathways.

ILPs and cancer chemoresistance

Resistance to drugs selectively affecting ILP signaling has been reported in many cancers, particularly in advanced cancers characterized by constitutively aggressive behavior, which are not influenced anymore by growth signals such as osteosarcoma (Avnet *et al*. 2009, Ulanet *et al*. 2010). For instance, in Ewing's sarcoma, an osteosarcoma type that mostly affects children (Garofalo *et al*. 2011), resistance to anti-IGF1R has been observed. Garofalo *et al*. (2011) have reported that chemoresistant cancer cells display an increased proliferative response to insulin accompanied by a decrease in insulin metabolic effects. Given the considerable physiological importance of insulin, drugs targeting ILPs were designed to affect IGF1R and hybrid receptors, sparing IR substrates, indicating that in cancers where IGF2 is overexpressed, chemoresistance due to the activation of anti-apoptotic signaling pathways via IR-A (Morcavallo *et al*. 2011, Wang *et al*. 2012) may be observed. Not surprisingly, chemoresistant Ewing's sarcoma cells have been reported to exhibit the ability to switch from IGF1/IGF1R to IGF2/IR-A receptor dependency, in order to maintain the sustained activation of Akt and ERK-1/2, which allows them to proliferate and migrate (Garofalo *et al*. 2011). Future anticancer therapy selectively targeting insulin substrates activated by IGF2 ligation to IR-A may abrogate the chemoresistance of cancer cells relying on the latter mechanism.

Furthermore, recent studies in medulloblastoma mouse models have pointed out PI3K signaling as a potential way of acquiring resistance to anticancer treatment (Buonamici *et al*. 2010). Such effect would be mediated through β-catenin signaling that has shown key roles in the chemoresistance to anticancer drugs in various cancer types (Fleming *et al*. 2008, Ashihara *et al*. 2009, Nwabo Kamdje *et al*. 2012, Seke Etet *et al*. 2012). In addition, another aspect to consider in the use of anti-ILP strategies for cancer treatment is the redundancy of growth factor signaling in cancer. For example, cancers driven mostly by other receptor types, such as EGF receptor (EGF-R), may be resistant to ILP targeting approach (Schmitz *et al*. 2012).

Notably, IGF1R signaling may confer chemoresistance to various anticancer agents in solid (Ma *et al*. 2008, Alvino *et al*. 2011, Rowinsky *et al*. 2011) and blood cancers (Ashihara *et al*. 2009, Rowinsky *et al*. 2011).

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Besides, IGFBP3 deficiency due to epigenetic gene silencing mediates the resistance to the anticancer drug cisplatin in non-small-cell lung cancer, through a mechanism involving the IGF1R/PI3K/Akt signaling pathway (Cortes-Sempere *et al*. 2012). Similarly, IGFBP7 may contribute to leukemia resistance to asparaginase but also to the pathogenic interactions between acute lymphoblastic leukemia stem cells and bone marrow stromal cells (Laranjeira *et al*. 2012).

Concluding remarks

In this review, we have examined recent studies of insulin resistance and their implications in carcinogenesis. While some of these data are conflicting, data from recent population-based studies have consistently suggested a strong link between antidiabetic treatment with drugs of the biguanide family and a decrease in cancer incidence and mortality (Suissa 2008, Kiri & Mackenzie 2009, Tan *et al*. 2011). As such, insulin, IGFs, and their receptors have been the subject of thorough investigations, particularly because of the ongoing worldwide epidemic of obesity, which is associated with complications like memory impairment (Schmoller *et al*. 2010, Kullmann *et al*. 2012), immune system deregulations, diseases like type 2 diabetes (Campbell 2011, Karagiannis *et al*. 2012), and cancer (Byers & Sedjo 2011, Spyridopoulos *et al*. 2012). IR-A and IGF1R mediate their effects through oncogenic PI3K/Akt, Ras/MAPK, and β-catenin signaling pathways, explaining at least in part their involvement in carcinogenesis, and the ability of overexpressed insulin and IGFs to increase cancer risk in obese subjects or in patients with a history of diabetes in first-degree relatives (see section Insulin-like peptides, insulin resistance, and cancer risk). Experimental evidence indicated that ILPs play a crucial role in cancer stem cell maintenance and chemoresistance, and accordingly, drugs targeting IGF1R have been developed and are currently in clinical trials. However, chemoresistance has been reported, particularly in advanced cancers that are less dependent on growing factors, and in cancer using redundant growth factors for their maintenance. A switch from IGF1/IGF1R to IGF2/IR-A signaling would explain at least in part several cases of chemoresistance to various anticancer drugs, besides IGF1R antagonists, indicating that drugs affecting IR-A or IGF2 expression may re-sensitize resistant cells to cancer therapy. Future research should focus on better characterizing the molecular mechanism linking ILPs in cancer pathogenesis, considering their potential for cancer biology understanding and the therapeutic implications.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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