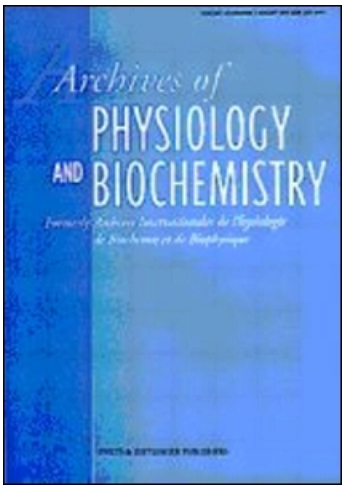

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REVIEW ARTICLE

The insulin-like growth factor-I receptor as an oncogene

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Abstract

The insulin-like growth factor-I receptor (IGF-IR) mediates the biological actions of both IGF-I and IGF-II. The IGF-IR is expressed in most transformed cells, where it displays potent antiapoptotic, cell-survival, and transforming activities. IGF-IR expression is a fundamental prerequisite for the acquisition of a malignant phenotype, as suggested by the finding that IGF-IR-null cells (derived from *IGF-IR* knock-out embryos) are unable to undergo transformation when exposed to cellular or viral oncogenes. This review article will focus on the underlying molecular mechanisms that are responsible for the normal, physiological control of IGF-IR gene expression, as well as the cellular pathways that underlie its aberrant expression in cancer. Examples from the clinics will be presented, including a description of how the IGF system is involved in breast, prostate, pediatric, and gynecological cancers. Finally, current attempts to target the IGF-IR as a therapeutic approach will be described.

Keywords: *Insulin-like growth factor-I (IGF-I); IGF-I receptor; targeted therapies; gene expression; cancer*

Introduction

The availability of highly sophisticated technologies, including "classical" genomic and proteomic approaches as well as novel microarray-based, high-throughput platforms with specific aims (e.g. micro-RNA detection, DNA methylation identification, single nucleotide polymorphism analysis, etc.), is having a huge impact in all areas of medicine, including the field of cancer research. Specifically, these techniques provide us with the opportunity to investigate physiological and pathological processes at various levels of regulation, and to tackle biological questions in an integrative and unbiased fashion. The insulin-like growth factors (IGFs) constitute a group of cellular and secreted factors with important roles in multiple biological systems. Since their discovery in the mid-1950s, IGFs have attracted the attention of developmental biologists, endocrinologists, oncologists, and others (LeRoith *et al.*, 2001a; Salmon & Daughaday, 1957). In recent years, the vast amount of information generated by experimentalists, clinicians, and epidemiologists led to the development of molecular tools aimed at targeting the IGF axis as a clinically relevant therapeutic target in cancer and, potentially, other conditions (Hartog *et al.*, 2007; Riedemann & Macaulay, 2006). The aim of this review article is to summarize evidence accumulated over the last 20 years, which identified the IGF-I receptor (IGF-IR) as a potential cellular oncogene. In addition, various targeted therapies and several specific cancers in which the IGF axis is involved will be discussed in more detail.

The IGF system: Ligands, receptors and binding proteins

The IGF ligands comprise IGF-I, IGF-II, insulin, and a number of non-classical ligands whose biological role is still controversial (Werner & LeRoith, 2000) (Table 1). At the cellular level, IGF-I is a progression factor that is required by the cell to advance through the various phases of the cell cycle. The concentration

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Table 1. IGF system components.

IGF ligands
Insulin
IGF-I
IGF-II
IGF receptors
Insulin receptor
IGF-I receptor
IGF-II/Mannose 6-phosphate receptor
Insulin receptor-related receptor
Insulin/IGF-I hybrid receptor
IGF-binding proteins
IGFBP1 to IGFBP6
IGFBP-related proteins
IGFBP proteases

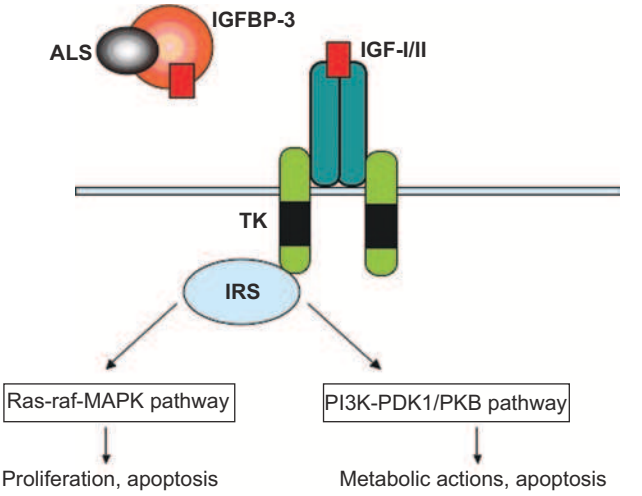

Figure 1. The biological actions of IGF-I are mediated by the IGF-IR and modulated by IGFBPs. IGF-I and IGF-II bind to the extracellular domain of the IGF-IR and induce autophosphorylation of the tyrosine kinase (TK) domain of the receptor. The bioavailability of the ligands is controlled by a family of IGF-binding proteins (IGFBP1-6). The most abundant IGFBP in serum is IGFBP3, which circulates as a ternary complex including the BP itself, the ligand, and an acid-labile subunit (ALS). The affinity of the IGFBPs for the ligand is usually higher than that of the IGF-IR. The ratio between free and IGFBP-bound IGF is important in determining the potency of the growth factor. Following activation of the IGF-IR, the insulin receptor substrates (IRSs) become phosphorylated, leading to activation of two main cascades, the ras-raf-MAP kinase and the PI3K-PDK1-Akt/PKB pathways.

of circulating IGF-I is mainly dependent on production by the liver, which is tightly controlled by growth hormone (GH) (LeRoith *et al.*, 2001b). In addition to its classical endocrine role, many extra-hepatic tissues, including the brain, kidney, stomach, and others produce IGF-I and/or IGF-II. At the organ level, IGFs display paracrine and autocrine modes of action, and are able to interact with other locally produced factors, including steroid hormones (Yee & Lee, 2000).

The IGF receptors comprise the insulin receptor (IR), IGF-IR, IGF-IIR, and several atypical receptors, including the insulin receptor-related receptor, and the IR-IGF-IR hybrid receptor (composed of an IR hemi-receptor linked to an IGF-IR hemi-receptor) (Nakae *et al.*, 2001). Accumulating evidence suggests that both IGF-I and IGF-II exert their activities *via* the IGF-IR, which signals mitogenic, anti-apoptotic, and transforming activities (Baserga *et al.*, 2003). The IGF-IR is a cell-surface heterotetrameric tyrosine kinase receptor coupled to several intracellular second messenger pathways, including the *ras-raf*-MAPK and PI3K signaling cascades (Figure 1). As described below, the IGF-IR is vital for cell survival, as illustrated by the lethal phenotype of mice in which the gene was disrupted by homologous recombination (Baker *et al.*, 1993; Liu *et al.*, 1993). In contrast, the IGF-IIR is a single chain receptor identical to the mannose-6 phosphate (M6P) receptor (Morgan *et al.*, 1987). The IGF-II/M6PR targets IGF-II for lysosomal degradation and thus reduces the bioavailability of the highly mitogenic IGF-II. Consistent with a putative tumour suppressor role, the IGF-II/M6PR is mutated or deleted in several cancers (Leboulleux *et al.*, 2001). In addition, most available evidence indicates that the IGF-II/M6PR is not involved in intracellular signalling. Some of the bioactivities of IGF-II are mediated via a particular isoform of the IR (IR-A), which is generated by alternative splicing of the IR gene (Frasca *et al.*, 1999).

The biological actions of IGF-I/II are modulated by a family of IGF-binding proteins (IGFBPs) and IGFBPs-related proteins (Baxter, 2000; Cohen, 2006). IGFBPs bind IGFs with an affinity higher than that of IGF-IR and usually inhibit IGF metabolic and proliferative actions by preventing from the ligand to interact with the receptor. Some IGFBPs, however, display IGF-potentiating effects. It seems that the ability of IGFBPs to display both IGF-stimulatory and inhibitory activities is dictated by a number of factors, including the tissue-specific distribution of particular IGFBPs (membrane bound, intercellular matrix bound, etc), and the ratio between free (active) IGF-I and IGFBP-bound IGF-I. In the serum, the majority of circulating IGFs are found in a ternary complex with IGFBP3 and an acid-labile subunit. This complex modulates IGF action by protecting the growth factors from proteolysis, thus prolonging their half-lives in the circulation. The relative contribution of endocrine *versus* tissue IGF-I and IGF-II in growth control has been a cardinal question in the IGF field for many years (LeRoith *et al.*, 2001b). Our current view of the IGF system is modelled, to a large extent, on the basis of targeting studies in which specific IGF system components were disrupted (or overexpressed) in animal models, as described below.

The roles of the IGF axis in growth and development: Lessons from animal models

The role of the IGF axis in growth and development was demonstrated by the growth deficits of mice in which IGF components were disrupted by homologous recombination; IGF-I K.O. mice weighed about 60% of wild-type animals at the time of birth. In addition, IGF-I-disrupted mice exhibited very high perinatal mortality, delayed ossification, underdeveloped muscles and lungs, as well as infertility (Baker *et al.*, 1993; Liu *et al.*, 1993; Powell-Braxton *et al.*, 1993). Similarly, targeted disruption of the IGF-II gene resulted in mice weighing 60% of their normal littermates at the time of birth (DeChiara *et al.*, 1990). These mice, however, developed into normal and proportionate fertile dwarfs.

The most severe phenotype was the one exhibited by IGF-IR K.O. mice (Liu *et al.*, 1993). Disruption of this gene resulted in small (more than a 50% reduction in weight) animals that died in the immediate postnatal period from respiratory failure. These animals exhibited generalized developmental abnormalities, including hypoplasia, abnormal skin formation, delayed bone development, and abnormal central nervous system morphology.

IGF-IR and transformation

The key role of the IGF-IR in oncogenic transformation is illustrated by the results of experiments showing that fibroblasts derived from mouse embryos in which the IGF-IR was disrupted by homologous recombination (R^-) cannot be transformed by any of a number of oncogenes (including the SV40 large T antigen, activated *ras*, etc.) (Morrione *et al.*, 1995; Sell *et al.*, 1993). Re-introduction of a functional receptor renders R^- cells susceptible to the transforming activities of these oncogenes. However, certain exceptions to this general paradigm have been reported. For instance, transfection of the GTPase-deficient mutant human G_{a13} resulted in transformation of R^- cells. These results indicate that G_{a13} can induce cellular transformation through pathways independent of IGF-IR (Liu *et al.*, 1997).

Exogenous over-expression of the IGF-IR in fibroblasts results in a ligand-dependent, highly transformed phenotype, which includes the formation of tumours in nude mice (Kaleko *et al.*, 1990). On the other hand, abrogation of the IGF-IR signalling pathway using IGF-IR antibodies results in a drastic reduction in the proliferation of melanoma, breast, haematopoietic, colorectal, neuroblastoma, and Wilms' tumour cells (Werner & LeRoith, 1996). An intact tyrosine kinase domain is fundamental in order for the IGF-IR to exert its potent anti-apoptotic and transforming activities. Interestingly, the modes of action of a number of oncogenes depend on their ability to phosphorylate the IGF-IR. Thus, transformation by $pp60^{src}$, the protein encoded by the *src* oncogene of Rous sarcoma virus, results in the constitutive phosphorylation of the IGF-IR β subunit (Peterson *et al.*, 1994). It has been estimated that approximately 10–50% of the receptors are phosphorylated in the un-stimulated *src*-transformed cell. Addition of IGF-I synergistically increased the extent of phosphorylation of the receptor. These results are consistent with the notion that $pp60^{src}$ alters growth regulation by rendering the cells constitutively subject to a mitogenic signal.

The complexity of the IGF axis is further revealed by the phenotypes of mice with tissue-specific deletions of the IGF-IR gene. For example, conditional deletion of the gene in the dorsal and lateral prostate led to activation of the ERK1/2 pathway and caused cell autonomous proliferation and hyperplasia. Moreover, persistent loss of IGF-IR expression in the gland induced p53-regulated apoptosis and cellular senescence rescue programs, predicting that titration of IGF-IR signalling might facilitate growth of tumours with compromised p53 activity (Sutherland *et al.*, 2008).

The role of the IGF axis in cancer: Epidemiological evidence

The IGF system has been implicated in several different human malignancies, including various epithelial cancers, sarcomas, multiple myeloma, melanoma, and childhood cancers (Sachdev & Yee, 2007; Werner & LeRoith, 1996). Initially, small prospective epidemiological studies failed to show a link between IGF-I and breast (Mantzoros *et al.*, 1999) or prostate (Kanety *et al.*, 1993) cancers. However, more recent large studies have suggested that high circulating IGF-I levels and/or low IGFBP3 levels are associated with increased risk of several cancers including breast (Allen *et al.*, 2005; Hankinson *et al.*, 1998), prostate (Chan *et al.*, 1998; Stattin *et al.*, 2000), lung (Yu *et al.*, 1999), colorectal (Ma *et al.*, 1999; Palmqvist *et al.*, 2002), endometrial (Petridou *et al.*, 2003), and bladder (Zhao *et al.*, 2003), supporting a possible paracrine role of the IGF system in tumourigenesis. Furthermore, the negative correlation between IGFBP3 levels and cancer risk is consistent with a protective role of IGFBP3 (i.e. high IGFBP3 concentrations may lead to reduced *free* IGF-I values). A comprehensive meta-analysis by Renehan *et al.* (2004) concluded that, despite certain controversies, circulating IGF-I values are positively associated

with cancer risk in prostate, pre-menopausal breast, and colorectal cancer.

Increased local expression of IGF-I, IGF-II, IGF-IR or a combination of them have been documented in various malignancies, with usually positive correlations between IGF-I/IGF-II levels and tumour progression (Samani *et al.*, 2007; Werner & LeRoith, 1996). However, conflicting results were reported in a number of studies and, therefore, the clinical and prognostic significance of IGF-IR expression levels in human cancer remains unclear (Schnarr *et al.*, 2000; Tennant *et al.*, 1996). These discrepancies may have been due to differences in study methods including tissue preservation techniques, sample sizes, and data analysis methods.

IGF-IR and tumour metastasis

IGF-IR signalling plays an important role at critical steps of the metastatic cascade, including cell adhesion, migration, invasion, angiogenesis, and metastatic growth at distant organ sites (Samani *et al.*, 2007). Dunn *et al.* (1998) have shown that impairment of IGF-IR function by a dominant negative mutant, 486STOP, significantly suppressed adhesion and invasion of two different oestrogen receptor (ER)-negative breast cancer cell lines. Furthermore, *in vivo* studies revealed that functional impairment of the IGF-IR did not suppress the growth of the primary tumour, but significantly decreased tumour metastases to the lungs, liver, lymph nodes, and lymph vessels. In addition, Reinmuth *et al.* (2002) showed that colon cancer cells expressing a dominant-negative IGF-IR failed to produce liver metastases after direct injection into the liver, suggesting that the IGF-IR can regulate tumour metastases independently of tumour growth.

These preclinical observations, demonstrating that the IGF-IR plays an important role in growth, angiogenesis, and metastasis, were further supported by clinical studies in different human malignancies. More specifically, in a study of 56 prostate cancer cases, Liao *et al.* (2005) showed that IGF-I and IGF-II expression levels were elevated in high grade, as compared to low grade tumours. Similarly, Hakam *et al.* (1999) found an increase in IGF-IR expression during progression from colonic adenoma to colorectal adenocarcinoma and metastases, and demonstrated that IGF-IR expression was correlated with the stage of the disease. On the other hand, Shiono *et al.* (2006) found no correlation between IGF-IR expression and long-term prognosis in a study of 86 colorectal carcinoma metastases. Likewise, Kornprat *et al.* (2006) found increased IGF-IR expression in 52 out of 55 primary gallbladder carcinomas and in all 17 metastases, although no significant association with tumour stage, grade, or prognosis were detected. Finally, IGF-II gene expression was associated with high-grade epithelial ovarian cancer and was shown to be an independent predictor of poor survival (Sayer *et al.*, 2005).

Selected examples of IGF-IR involvement in human cancer

Breast cancer

Among all human cancers, breast tumour is the one in which the involvement of the IGF system was most extensively studied. Epidemiological, clinical, and *in vitro* and *in vivo* experimental evidence support a key role for the IGF axis in breast cancer development. Many components of the IGF axis are altered in the circulation of breast cancer patients. Moreover, the expression of IGF ligands, receptors, and binding proteins is changed in breast cancer tissue compared with normal breast tissue (Werner & LeRoith, 1996). Recent epidemiological studies have indicated that evaluation of IGF levels in breast cancer patients might be important both in terms of prognosis and diagnosis. However, the results of some of these studies are controversial. A number of systematic reviews and meta-analyses of prospective and case-control studies indicated a relationship between IGF-I and IGFBP-3 regarding breast cancer risk in pre-menopausal but not postmenopausal women (Fletcher *et al.*, 2005; Renehan *et al.*, 2004; Shi *et al.*, 2004; Sugumar *et al.*, 2004). However, a recent case-cohort study, which included 423 breast cancer cases and 1901 controls, reported that IGF-I and IGFBP-3 were positively associated with breast cancer risk in patients older than 50, but not in younger women (Baglietto *et al.*, 2007). Likewise, the European Prospective Investigation into Cancer and Nutrition (EPIC) study analysed data from 1081 patients and 2098 controls, and reported that high levels of IGF-I or IGFBP-3 are associated with a 40% increased risk for breast cancer in women older than 50 years of age, but not in younger women (Rinaldi *et al.*, 2006). Finally, another report from the prospective Nurses' Health Study II found no association between circulating IGF-I, IGFBP-1, and IGFBP-3 levels and breast cancer risk in a large cohort of premenopausal women (Schernhammer *et al.*, 2006). We assume that contradictory data between the various reports may stem from a number of variables, including the different analytical methods used (RIA, ELISA, extraction protocol, etc), population characteristics, age at diagnosis, nutritional status, etc.

In addition to epidemiological data, experimental evidence also implicates the IGF system in breast

cancer aetiology (Surmacz *et al.*, 1998; Yee & Lee, 2000). Activation of the IGF-IR protects breast cancer cells from apoptosis induced by a number of anti-cancer drugs (Dunn *et al.*, 1997). Consistent with its anti-apoptotic role, accumulating evidence shows that the IGF-IR gene is highly expressed (39–93%) in breast carcinomas (Happerfield *et al.*, 1997), yet the precise biological significance of over-expression levels remains controversial. Data have suggested lower levels of IGF-IR in benign lesions and normal breast tissue, compared with their malignant counterpart (Lee *et al.*, 1998; Peyrat *et al.*, 1988). However, a study by Schnarr *et al.* (2000) showed that IGF-IR is expressed at high levels in control tissues and in well and moderately differentiated breast carcinoma, but at significantly lower levels in poorly differentiated cancers. Several researchers have suggested that high IGF-IR levels may serve as a predictor of early recurrence of the disease (hence worse prognosis), whereas others consider high IGF-IR values as a marker of favourable prognosis (Papa *et al.*, 1993; Turner *et al.*, 1997).

A correlation between somatic IGF-IR expression and tumour suppressor BRCA1 status in breast cancer was recently described by Maor *et al.* (2007). IGF-IR levels were significantly higher in breast tumours of BRCA1 mutation carriers, compared with those from non-BRCA1 mutation carriers. Furthermore, infection of breast cancer cells with a wild-type BRCA1-encoding viral vector reduced endogenous IGF-IR levels. This could be a putative mechanistic explanation for the lower IGF-IR levels observed in tumours derived from non-BRCA1 mutation carriers and for the diminished mitogenic activity in wild-type BRCA1-overexpressing cells. Consistent with this model, a recent study showed that the levels of some IGF system components, including IGF-IR, in normal and tumour breast tissue were higher in individuals with a strong family history of breast cancer than in individuals without a family history (Voskuil *et al.*, 2004).

The key role of the IGF-IR as a mediator of IGF-I/II action in breast cancer was demonstrated by studies showing that IGF-IR blockage led to dramatic reductions in proliferation and other neoplasia parameters. Immunohistochemical analysis of primary breast tumours revealed that high IGF-IR levels were correlated with ipsilateral tumour recurrence following lumpectomy and radiation therapy (Turner *et al.*, 1997). In addition, high IGF-IR levels were associated with the development of resistance to herceptin, a monoclonal antibody against the extracellular domain of HER2–neu used in the treatment of ERBB2-overexpressing breast cancer (Lu *et al.*, 2001). Finally, ER status has been shown to have a major effect on IGF-IR levels and action (Oesterreich *et al.*, 2001). Thus, MCF-7-derived clones selected for loss of ERα by long-term oestrogen withdrawal exhibited reduced IGF-IR levels in comparison with the ERα-positive native MCF-7 cells. Re-expression of ERα in ERα-depleted clones significantly increased IGF-IR gene expression and IGF action.

Prostate cancer

A significant amount of data has been accumulated suggesting that the IGF system plays an important role in normal prostate gland growth and development as well as in prostate cancer initiation and progression. Several prospective studies in the late 1990s suggested that high circulating IGF-I levels were associated with an increased risk of prostate cancer (Grimberg & Cohen, 1999; Monti *et al.*, 2007). A meta-analysis concluded that the relative risk was similar in magnitude to that conferred by testosterone (Shaneyfelt *et al.*, 2000). A second meta-analysis of 14 case-control studies showed that circulating levels of IGF-I and IGFBP-3 were significantly higher in prostate cancer patients (Shi *et al.*, 2001). Interestingly, in a prospective study, Djavan *et al.* (1999) found that the IGF/PSA ratio was superior to IGF-I or PSA measurements alone for predicting prostate cancer risk. In another prospective study, Chan *et al.* (1998) found that plasma levels of IGF-I and IGFBP-3 were predictors of advanced-stage prostate cancer but not of early-stage cancer. However, in a cross-sectional study, Latif *et al.* (2007) did not find a correlation between IGF-I and IGFBP-3 concentrations and cancer risk. In a recent prospective case-control study of 727 incident prostate cancer cases and 887 matched controls, it was concluded that there was no clear overall association between IGF-I and IGFBP-3 and the IGF:IGFBP-3 ratio and prostate cancer risk; however, this ratio was associated with increased risk in obese men (BMI> 30) (Weiss *et al.*, 2008).

The data regarding the expression of IGF pathway components in prostate cancer are controversial. Wang & Wong (1998) showed that sex hormone-induced prostatic carcinogenesis in a noble rat model is regulated by IGF-I. Furthermore, transgenic mice expressing IGF-I in the basal prostate epithelial cells showed IGF-IR activation and prostate tumorigenesis (DiGiovanni *et al.*, 2000). Hellawell *et al.* (2002) in a study of 54 primary prostate samples, showed that IGF-IR was significantly up-regulated at the protein and mRNA levels, compared with benign prostatic epithelium. In addition, in a study using frozen tissue sections, widespread IGF-IR expression was found in normal prostate, prostate cancer, and metastases with more intense staining in the stromal

tissue surrounding the tumour, compared with the surrounding benign tissue (Ryan *et al.*, 2007). Other profiling studies, however, did not find appreciable differences in IGF-IR levels between normal prostate and prostate cancer (Dhanasekaran *et al.*, 2001).

Of particular interest, during transformation of prostate epithelial cells from a benign to a metastatic state, a marked reduction in IGF-IR levels was reported (Plymate *et al.*, 1997). Chott *et al.* (1999) showed that IGF-IR expression is decreased in primary tumours, compared with benign tissues, and is largely lost in bone metastases. It has been postulated that the decreased expression results from transcriptional repression of the IGF-IR gene, which may be due in part to increased expression of the Wilms' tumour suppressor (WT1) in metastatic prostate cancer (Damon *et al.*, 2001). However, other studies do not support the concept of reduced IGF-IR levels and action in metastatic cancer (Hellawell *et al.*, 2002). Finally, multiple preclinical and clinical investigations are underway to evaluate the potential value of IGF-IR targeting in prostate cancer. GnRH antagonists and somatostatin analogues have been shown to have anti-proliferative effects in prostate cancer (Dimopoulos *et al.*, 2005; Gonzalez-Barcena *et al.*, 2003). The anti-tumoral activity of these agents *in vitro* and *in vivo* was partially attributed to the reduction in GH and IGF-I levels. Targeted therapies using IGF-IR monoclonal antibodies are described below.

Pediatric tumours

The role of the IGF system in the biology of Ewing, rhabdomyosarcoma, Wilms', and other pediatric tumours has been the focus of intensive investigation (Toretsky *et al.*, 1997; Toretsky *et al.*, 2001; Wang *et al.*, 1998). In Ewing sarcoma, IGF signalling has been reported to play a major role in the proliferation and malignant behaviour of tumours (Scotlandi *et al.*, 1998), and the IGF-IR was identified as the main growth factor receptor in Ewing sarcoma cell lines. Martins *et al.* (2006) recently reported dose-dependent inhibition of cell proliferation with G1 phase blockage and apoptosis in Ewing tumour cell lines treated with a small-molecule IGF-IR tyrosine kinase inhibitor (ADW742). Moreover, combining chemotherapy agents resulted in a synergistic effect. These *in vitro* observations, demonstrating the role of the IGF-IR in growth and malignant behaviour of Ewing sarcoma, have been further substantiated by *in vivo* studies. For example, Manara *et al.* (2007) found a marked *in vivo* inhibition of migration, metastasis, vasculogenicity, and angiogenesis after treatment of Ewing sarcoma cells with another IGF-IR kinase inhibitor (NVP-AEW541). Notably, in this study, the athymic mice treated with the compound had various side effects, including hypoglycaemia, uraemia, and weight loss.

The key role of the IGF-IR in the biology of Wilms' tumours is illustrated by the fact that IGF-IR mRNA levels were almost six-fold higher in Wilms' tumour than in normal adjacent kidney tissue (Werner *et al.*, 1993). In addition, IGF-IR expression in the tumours was negatively correlated with the expression of WT1, a zinc-finger transcription factor whose mutation is a key event in the aetiology of the disease. Functional and physical correlations between WT1 and the IGF-IR gene indicated that, consistent with its tumour-suppressor role, WT1 expression inhibited IGF-IR gene transcription (Werner & Maor, 2006). Finally, Shevah & Laron (2007) analysed the prevalence of malignancy in 222 patients with congenital IGF-I deficiency and 338 first- and second-degree relatives. None of the IGF-I-deficient patients had cancer in an age range between 3–78 years, whereas 9–24% of the family members had a history of malignancy. These epidemiological results are consistent with the concept that the IGF-I axis has a fundamental role in cancer development.

Gynaecologic cancers

A number of studies identified the IGF system as an important player in the development of gynaecologic tumours. For example, Hirano *et al.* (2004) reported significantly higher expression of IGF-IR in a study of 46 endometrial (91%), 32 cervical (87%), and 20 ovarian (95%) cancers. A description of the role of the IGF-IR in specific gynaecologic cancers follows.

Cervix cancer

Steller *et al.* (1995) found an elevation in IGF-II, but not IGF-I, mRNA levels following epidermal growth factor (EGF) stimulation in the cervical cancer cell line HT-3, and suggested that IGF-II plays a central role in mediating cervical cancer. Furthermore, the elevation in IGF-II levels was prevented by IGFBP-5, whereas an anti-sense oligonucleotide against IGF-II inhibited the proliferative response to EGF. Based on these results, the authors postulated the existence of a cross-talk between the EGF and IGF systems of growth factors and suggested that autocrine production of IGF-II may mediate the mitogenic effect of EGF in cervical cancer. In addition, analyses of the incidence of loss of heterozygosity and abnormal imprinting of the H19 and IGF-II genes in invasive cervical carcinomas revealed that both genes, *via* deletions or abnormal imprinting or both, play a crucial role in these

neoplasms (Douc-Rasy *et al.*, 1996). In a follow-up report, Steller *et al.* (1996) reported over-expression of the IGF-IR in primary cervical cancer cell cultures and cell lines, compared with normal cervical cells.

In a more recent study, Mathur *et al.* (2003) demonstrated high IGF-II levels in cervical cancer compared with normal cervical biopsies. The authors also reported a significant correlation between IGF-II levels in the tumours and pelvic lymph node metastasis. Interestingly, small nests of malignant cells were identified in the lymph nodes by using IGF-II as a marker. In addition, serum levels of IGF-II and IGFBP-3 were evaluated in patients with normal cervix, cervical intra-epithelial neoplasia (CIN), or cervical cancers. Interestingly, serum IGF-II levels were elevated in patients with CIN and cervical cancers, compared with normal levels in patients with normal cervix and successfully treated CIN and cervical cancers. Serum IGF-BP3 showed a significant decrease at advanced stage disease. Finally, there was a positive correlation between vascular endothelial growth factor-C (VEGF-C) and IGF-II and a negative correlation between IGFBP-3 and VEGF-C (Mathur *et al.*, 2005).

Endometrial cancer

In the uterus, cyclic changes in IGF-I expression and signalling play an important role in regulating the transition of the pre-menopausal endometrium through proliferative, secretory, and menstrual cycles. In addition, a number of studies showed a correlation between components of the IGF system and endometrial cancer risk. For example, Ayabe *et al.* (1997) reported higher IGF-I and lower IGFBP-1 levels in postmenopausal patients with endometrial cancer compared to controls. Petridou *et al.* (2003), in a study of 84 endometrial cancer patients and 84 control women, reported that endometrial cancer was positively associated with IGF-II blood levels and inversely associated with IGF-I. In contrast, two large studies reported different results regarding serum levels of IGF-II and IGFBPs. Weiderpass *et al.* (2003), in a study including 288 endometrial cancer patients and 392 control women, found no correlation between cancer risk and serum IGF-I, IGFBP-1, and IGFBP-3 levels. Lacey *et al.* (2004), in a study of 405 endometrial cancer patients and 297 control women, reported that cancer was inversely associated with serum IGF-II and IGFBP-3. Consistent with IGF-IR having a central role in endometrial cancer, McCampbell *et al.* (2006) reported a significant increase in IGF-IR expression in biopsies from hyperplastic endometrium and endometrial carcinoma compared to proliferative endometrium. Likewise, Hirano *et al.* (2004) reported high expression of IGF-IR in all gynaecological cancers, with mRNA expression in 91.3% of the endometrial cancers.

Ovarian cancer

IGFs and their receptors play key roles in regulating the normal biology of ovarian epithelial cells and have been implicated in the transformed phenotype of ovarian carcinoma cells (Kalli & Conover, 2003). RNase protection assays revealed the presence of IGF-I and IGF-IR mRNAs in 100% of freshly isolated cancer specimens (Waksmanski *et al.*, 2001). IGF-I, IGF-II, and the IGF-IR have also been shown to be produced *in vitro* by ovarian cancer cell lines and various ovarian cancer cell lines display autocrine growth loops mediated through the IGF-IR (Resnicoff *et al.*, 1993). Using qRT-PCR, Sayer *et al.* (2005) found significantly higher IGF-II mRNA levels in 109 epithelial ovarian cancers compared with eight normal ovaries. Moreover, high IGF-II gene expression was associated with high-grade advanced stage disease and poor survival.

Two prospective studies reported a 2- to 5-fold increased ovarian cancer risk among women less than 55 years old at diagnosis when comparing the top versus bottom tertiles of IGF-I levels (Lukanova *et al.*, 2002). On the other hand, in several retrospective studies, serum IGF-I levels in patients with malignant ovarian tumours were lower than in controls (Bese & Nomir, 2001). Moreover, a recent nested case-control study of 222 ovarian cancer cases and 599 controls reported that the relative risk when comparing the top versus bottom quartiles of IGF-I was 0.56 (Tworoger *et al.*, 2007). The risk did not differ regarding age at diagnosis and no association was found between IGFBP-3, IGFBP-2, and the ratio of IGF-I to either binding protein or ovarian cancer risk. Finally, recent studies showed that a small molecule IGF-IR inhibitor had anti-proliferative activity in ovarian cancer cells (Gotlieb *et al.*, 2006).

Targeted therapy

The IGF-IR is emerging as one of the most promising molecular targets in cancer treatment. Multiple approaches are being utilized to abrogate IGF-IR signalling *in vitro* and *in vivo*. These approaches include dominant negative mutants, kinase defective mutants, anti-sense oligonucleotides, anti-sense expression plasmids, soluble receptors, IGF-BPs, antibodies against IGF-I and IGF-II, IGF-IR blocking antibodies, siRNA against IGF-IR mRNA and, more recently, a family of IGF-IR kinase inhibitors (Hofmann & Garcia-Echeverria, 2005; LeRoith & Helman, 2004).

In vitro and *in vivo* studies demonstrated that interfering with IGF-IR activation results in inhibition of tumour proliferation and metastases in multiple types of cancer as well as increased sensitization to chemotherapy and radiation therapies. A description of selected approaches follows.

IGF-IR blocking antibodies

Antibodies against IGF-IR were shown to prevent ligand-induced activation and to induce receptor internalization and degradation by endocytosis. As a result, signalling is abrogated (Sachdev & Yee, 2007). The feasibility of this targeting approach was first demonstrated using a mouse monoclonal antibody directed against the α-subunit of IGF-IR (α-IR3) (Kull *et al.*, 1983). This antibody showed significant *in vitro* and *in vivo* growth inhibition of many types of cancers, including breast (Arteaga *et al.*, 1989), rhabdomyosarcoma (Kalebic *et al.*, 1994), Ewing sarcoma (Scotlandi *et al.*, 1998), and non-small cell lung cancer (Zia *et al.*, 1996). In recent years, several IGF-IR antibodies have been developed and some of them are currently in phase I and II clinical trials (Hartog *et al.*, 2007). For example, monoclonal antibody EM164 was shown to inhibit IGF-I/II-stimulated proliferation and survival of diverse cancer cell lines. Furthermore, its anti-tumoral effect was enhanced by combined treatment with a cytotoxic agent (Maloney *et al.*, 2003). Similarly, Wu *et al.* (2005). In a recent study using a human prostate cancer xenograft model, showed that treatment with IM Clone's A12 antibody markedly decreased tumour size and also augmented the inhibition of docetaxel regarding tumour growth (Wu *et al.*, 2006). It has been suggested that antibody A12 blocks signalling by two mechanisms: (1) abrogation of ligand binding, and (2) induction of receptor internalization and degradation (Gennigens *et al.*, 2006).

Several *in vivo* studies evaluated the anti-tumour effect of anti-IGF-IR as monotherapy as well as in combination with chemotherapy, radiotherapy, or additional antibodies. Given the large homology between IR and IGF-IR, the potential effect of IGF-IR antibodies on IR signalling is of special concern. In a number of studies IGF-IR antibodies were shown to co-target or alter IR function, leading to insulin resistance and adverse effects on glucose and carbohydrate metabolism. On the other hand, IR targeting could potentially become an advantage because specific inhibition of the IR in the tumour (in particular the IR-A isoform) could add to the effective anti-tumoral activity (Hofmann & Garcia-Echeverria, 2005). Preliminary results from phase I trials in patients with advanced cancer treated with Pfizer's CP-751,871 or IM Clone's A12 antibodies showed only infrequent mild transient hyperglycaemia with no dose-limiting toxicity (Fong *et al.*, 2006; Higano *et al.*, 2006).

Small molecule kinase inhibitors

In addition to IGF-IR antibodies, a series of small-molecule IGF-IR kinase inhibitors have been used in experimental studies demonstrating tumour growth inhibitory properties. For example, Mitsiades *et al.* (2004) reported *in vitro* and *in vivo* anti-tumour activity of the IGF-IR kinase inhibitor NVP-ADW742 in multiple myeloma. Cellular kinase activity assays have shown that this compound has above 16-fold more potent inhibitory activity against IGF-IR than IR. Similarly, Garcia-Echeverria *et al.* (2004) reported *in vivo* anti-tumoral activity of the NVP-AEW541 compound in the MCF-7 and NWT-21 cell lines. This orally bio-available compound also inhibited IGF-IR signalling in tumour xenografts and significantly reduced the growth of IGF-IR-driven fibro-sarcomas. In addition, Scotlandi *et al.* (2005) reported that NVP-AEW541 effectively inhibited the *in vitro* tumour growth of Ewing sarcoma and displayed a synergistic effect with combined chemotherapy. Hopfner *et al.* (2006) showed *in vitro* growth inhibition of gastrointestinal neuro-endocrine tumours and hepatocellular carcinoma cells by NVP-AEW541, both alone and in combination with chemotherapy.

Recently, Haluska *et al.* (2006) reported the *in vitro* growth inhibition of colon (Colo205), ovarian (OV202), and MCF-7 breast cancer cells, as well as the *in vivo* growth of a mouse xenograft, using a dual IGF-IR/IR kinase inhibitor, BMS-554417. This small molecule inhibited both IR and IGF-IR with similar potency. However, at the most effective dose tested, transient hyperglycaemia and supra-physiologic elevation of secreted insulin was observed. In addition, Gotlieb *et al.* (2006) showed that ovarian cancer cell lines (OVCAR3 and OVCAR4) produce IGF-I and IGF-II and express IGF-IR, supporting the existence of an IGF autocrine loop in ovarian cancer. The inhibitory activity of NVP-AEW541 in these cell lines was associated with decreased Akt phosphorylation and increased PARP cleavage. Finally, another selective inhibitor of the IGF-IR tyrosine kinase is picropodophyllin (PPP). Importantly, PPP efficiently blocked IGF-IR activity and induced apoptosis and tumour regression in a xenograft mouse model (Girnita *et al.*, 2004).

IGF binding proteins

As mentioned above, a key mechanism for regulating IGF bioactivities involves the high-affinity IGFBPs,

which both in the circulation and in the extracellular environment modulate the activities of the IGFs (Hwa *et al.*, 1999). All six high-affinity IGFBPs have been shown to inhibit IGF actions, whereas IGFBP-1, -3, and -5 also exhibit IGF potentiating effects. Interestingly, it has become increasingly clear that certain IGFBPs have IGF-independent activities, suggesting that they can induce apoptosis and modulate cell survival in the absence of the ligand (Oh, 1998). IGFBPs were shown to inhibit tumour growth *in vitro* and *in vivo*. Yee *et al.* (1994) showed that IGFBP-1 inhibits IGF-I-induced growth in MCF-7 breast cancer cells by interrupting the interaction between IGF-I and its receptor. In addition, treatment of human cervical carcinoma and osteosarcoma cells with recombinant IGFBP-1 induced significant growth inhibition. In prostate cancer cells, IGFBP-related protein-1 was found to alter the cell cycle kinetics by arresting the cells at the G1 phase (Sprenger *et al.*, 2002). Finally, increased expression of endogenous IGFBP-3 or treatment with a recombinant human IGFBP-3 was shown not only to inhibit cancer cell growth in a variety of experimental systems but also to enhance the efficacy of radiation, pro-apoptotic, and chemotherapeutic agents (Burger *et al.*, 2005).

IGF-IR antisense oligonucleotides

Anti-sense oligonucleotides (ASO) against IGF-IR mRNA were shown to result in reduced IGF-IR levels and inhibition of IGF signalling pathways in multiple cancer types, including breast, prostate, lung, CNS, and bladder (Hellawell *et al.*, 2003; Neuenschwander *et al.*, 1995; Sachdev & Yee, 2007). A pilot study including 12 patients investigated the effect of *ex vivo* treatment of autologous malignant astrocytoma with ASO to IGF-IR. Results of this study showed that ASO induced apoptosis and a host response *in vivo* without unusual side effects (Andrews *et al.*, 2001). Interestingly, subsequent radiographic and clinical improvements were also observed.

Anti-IGF-IR in combination therapy

Therapies directed against the IGF-IR were shown to enhance the cytotoxic effects of conventional treatments. Thus, Rochester *et al.* (2005) showed that siRNA against IGF-IR enhanced the sensitivity to various DNA-damaging agents, including ionizing radiation, in prostate cancer. Interestingly, the authors found no sensitization to paclitaxel or 5-fluorouracil treatment, two agents that do not damage DNA, suggesting that chemo-sensitization results from a DNA damage response. In addition, there is evidence of cross-talk between the IGF-IR and ER signalling pathways. Thus, it has been suggested that IGF-IR therapy in breast cancer might be most effective when administered along with agents targeting the ER such as tamoxifen, selective ER modulators, or aromatase inhibitors (Oesterreich *et al.*, 2001; Yee & Lee, 2000). Combined treatment of human breast cancer xenografts with a chimeric humanized IGF-IR antibody (scFv-Fc) and tamoxifen was more effective in inhibiting tumour growth than scFv-Fc or tamoxifen alone (Ye *et al.*, 2003). Consistent with this notion, Gotlieb *et al.* (2006) demonstrated that treatment with a small molecule IGF-IR kinase inhibitor sensitized ovarian cancer cells to cisplatin.

Recent *in vivo* studies provided additional support for combination therapy. Treatment with CP-751,871, a humanized IGF-IR antibody, and 5-fluorouracil showed significantly greater anti-tumoral activity than 5-fluorouracil alone in a xenograft colon cancer model (Cohen *et al.*, 2005). Treatment of mice bearing small cell lung cancer cells with humanized anti-IGF-IR h7C10 induced significant growth inhibition and lifespan prolongation in combination with vinorelbine or an EFGR antibody (Goetsch *et al.*, 2005). In addition, Wang *et al.* (2006) demonstrated that treatment with antibody A12 produced an additive effect to irinotecan *in vitro* and *in vivo*. Similarly, Wu *et al.* (2007) reported marked tumour burden decrease and survival prolongation using combined therapy with A12 and other drugs (bortezomib, melphalan) in a multiple myeloma xenograft model. Taken together, these data support the conclusion that IGF-IR targeting has tremendous potential for cancer therapy, both alone and in combination with chemotherapy or other targeted therapies.

Conclusions

The IGF-IR plays a crucial role in normal development as well as in establishing and maintaining the malignant phenotype. Over-expression of the IGF-IR gene constitutes a common theme in many human cancers, with some tumours exhibiting reduced receptor levels at advanced stages. In this review, we have presented evidence demonstrating that the aetiology of several neoplasms is closely linked to the IGF system. A better understanding of the complex machinery underlying the regulation of the IGF system will improve our ability to develop effective treatment modalities for those conditions in which the IGF system is involved.

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