EUROPEAN JOURNAL OF CANCER 43 (2007) 1895–1904

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Review

The insulin-like growth factor 1 receptor in cancer: Old focus, new future

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ARTICLE INFO

Article history:
Received 16 May 2007
Accepted 25 May 2007
Available online 10 July 2007

Keywords:
Insulin-like growth factor 1 receptor
Insulin receptor
Hybrid receptor
Tyrosine kinase inhibitors
Targeted therapy
Growth factor receptor
Antibody
Cancer

ABSTRACT

The importance of insulin-like growth factor 1 receptor (IGF-1R) signalling in malignant behaviour of tumour cells is well established. Currently, development of drugs targeting the IGF-1R as anticancer treatment is emerging. Several IGF-1R targeting strategies are being investigated in phases I and II clinical trials. Interactions of IGF-1R with insulin receptor, however, might complicate efficiency and tolerability of such drugs. This review describes mechanisms, recent developments and potential limitations of IGF-1R antibodies and tyrosine kinase inhibitors.

1. Introduction

A new class of drugs targeting the insulin-like growth factor receptor type 1 (IGF-1R) is in an advanced stage of clinical development. The choice of this receptor tyrosine kinase (RTK) as a target for anticancer therapy is driven by a multitude of *in vitro* and *in vivo* data supporting a powerful pro-survival signal of this receptor in tumour growth and development. In general, RTKs execute key roles in tumour progression and therefore represent attractive targets for anticancer therapy.[1] Indeed, since the introduction of imatinib in the treatment of chronic myeloid leukaemia and GIST in 2000, RTK targeting has successfully been applied in the treatment of various other tumour types as well (for a review, see Ref. 2).

The IGF-1R is different from most RTKs regarding some structural features, receptor-ligand interaction and downstream signalling. While most RTKs are mainly involved in autocrine and paracrine cell-to-cell signalling, IGF-1R signalling is also under endocrine control.[3] IGF-1R activation by insulin-like growth factor 1 (IGF-1) effectuates the growth stimulating effects of growth hormone (GH) in the target organs. Moreover, IGF-1R signalling is intimately connected to the metabolic functions of insulin.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.05.021

Due to the ubiquitous presence and body-wide physiologic function of IGF-1R, targeting its signalling may result in serious side effects. Especially interactions with the metabolic function of the insulin receptor (IR) need special attention.

This review aims to explore which anti-tumour effects could be accomplished by IGF-1R targeting drugs and potential limitations of such drugs, considering the mechanistic basis of IGF-1R function in normal physiology and cancer. We will discuss recent developments which show that some of the initial hesitations to develop IGF-1R targeting drugs for clinical use have been overcome. In addition, several potential applications of IGF-1R antibodies and tyrosine kinase inhibitors in various tumour types and in combination with conventional therapy will be described.

2. Structure and physiological function of the IGF-1R

The IGF-1R functions as a heterotetramer of two extracellular ligand binding α subunits and two β subunits comprising the transmembrane and tyrosine kinase domains.[1] Upon ligand binding a conformational change induces activation of the kinase. Several docking proteins, such as Src homology 2 domain-containing (Shc) protein and insulin receptor substrates (IRS1–4), are subsequently recruited to the phosphorylation sites in the cytoplasmic domain. Then the signal is propagated via the phosphatidylinositol-3-kinase (PI 3-kinase)/Akt and mitogen-activated protein (MAP) kinase pathways resulting in cell proliferation and inhibition of apoptosis. IGF-1R signalling can also induce differentiation, malignant transformation and regulate cell–cell adhesion (Fig. 1). A dynamic downstream signalling network of different phosphorylation sites of the receptor and cell-context specific recruitment and activation of signalling molecules regulates these different functions.[4] For example, while the tyrosine kinase domains are indispensable for all receptor functions and stimulate mitogenicity and motility of cells, phosphorylation at other cytoplasmic tyrosine residues confers additional capability for anchorage-independent growth and increases metastasising capacity of tumour cells.[5] More downstream, activation of docking protein IRS-1 favours proliferation while suppressing differentiation, whereas IRS-2 is involved in motility.[6,7] Furthermore, the IGF-1R can interact with steroid hormones and their receptors, other peptide growth factor receptors, extracellular matrix proteins, integrin receptors and cytokines, such as transforming growth factor-β.[3]

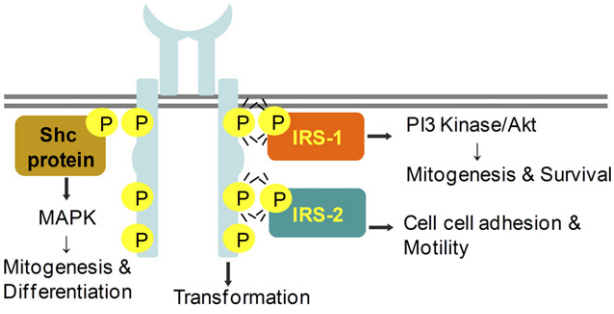

Fig. 1 – Schematic illustration of the IGF-1R and downstream pathways (P, phosphorylation site; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase).

The IGF-1R functions in a ligand-activated receptor-signalling system with the insulin receptor (IR) (Fig. 2). The IGF-1R is highly homologous to both splice variants of the IR (IR-A and IR-B), particularly in the cytoplasmic domain,[8] and these receptors use signalling pathways much similar to the IGF-1R.[9] The structural homogeneity allows formation of hybrid receptors (hybrid-R) in which an IGF-1R αβ-chain is connected to an IR-A or -B αβ-chain. When IGF-1R and IR are co-ex-

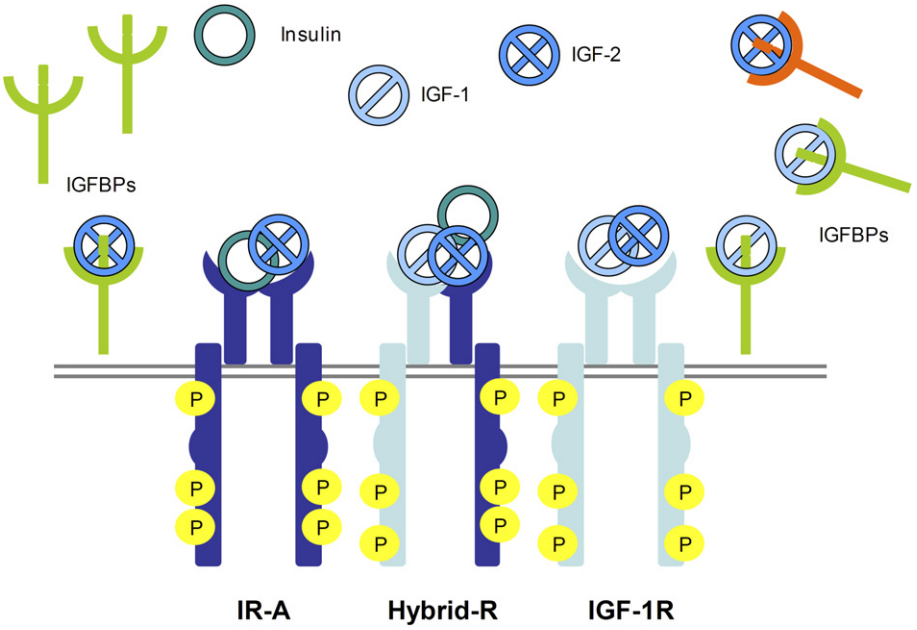

Fig. 2 – The ligand-activated receptor family of IGF-1R and IR. Schematic representation of ligands, receptors and regulatory binding proteins (IGFBPs). The situation of IR is depicted as for IR-A, the isoform with most functional overlap with the IGF-1R. In contrast to IR-B, IR-A binds IGF-2 and can perform IGF-like functions.

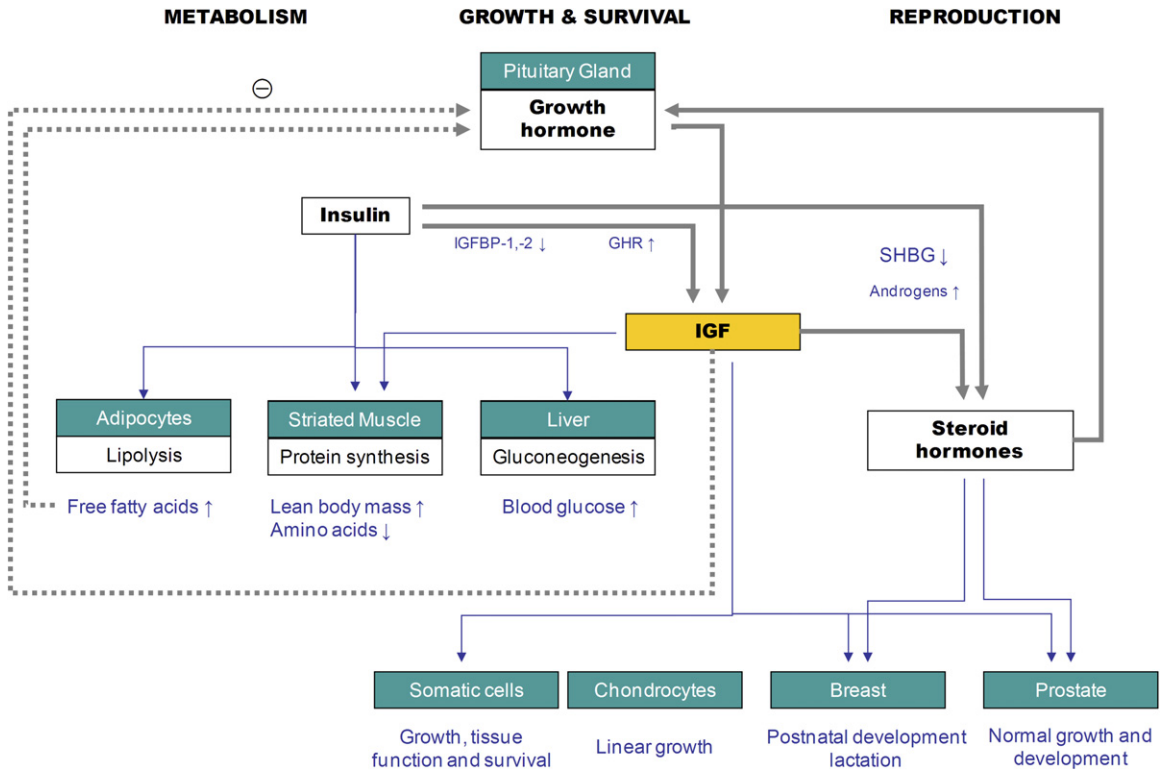

Fig. 3 – Endocrine regulation and function of IGF-1 and the connections with metabolic and reproductive functions through interaction with insulin and steroid hormones (IGFBP, IGF binding protein; GHR, growth hormone receptor; SHBG, sex hormone binding globulin).

pressed on the same cell, receptor hybrids form by random assembling and the least abundant receptor is drawn predominantly into hybrid-Rs.[8] The third receptor in the system is the IGF-2 receptor (IGF-2R), which is structurally and functionally unrelated to the IGF-1R and IR. The IGF-2R has no known signal transducing function, but it has a regulatory role in the IGF-1R system by degradation of IGF-2.[3]

IGF-1 is the principal ligand for the IGF-1R and hybrid-R. While IGF-1 and insulin are able to activate each other receptor only at high concentrations, IGF-2 is special in that it can bind the IGF-1R as well as the hybrid-R and IR-A with affinities approaching that of the cognate ligands.[10]

It is intriguing how IGF-1R and IR can accurately perform distinct cellular and physiological functions despite a very similar molecular architecture. IGF-1R and IR, however, do share some functional capabilities, IR-A can perform IGF-like functions and IGF-1R could partially compensate for loss of metabolic functions of the IR.[11] These functional similarities and dissimilarities are reflected in receptor expression and ligand availability. Both IGF-1R and IR are almost ubiquitously expressed, enabling a close connection. However, IR expression prevails in metabolic target organs, such as the liver, where IGF-1R levels are absent, while IGF-1R expression is high and IR low in e.g. fibroblasts.[8] Also, although the ligands share some similar affinities for receptor binding, the regulation of ligand bio-availability differs fundamentally. Insulin is under tight control of blood glucose levels and is excreted by the pancreas solely in periods of rising blood glucose levels. IGF-1 is produced under endocrine GH control in the liver as well as in somatic cells. In contrast to insulin and IGF-1, production of IGF-2 is autocrine and paracrine. A group of 6 IGF binding proteins (IGFBPs) tightly regulate stability of IGF-1 and IGF-2 in the circulation, transport to target tissues and interaction with the receptors, thereby preventing unlimited availability of IGF-1 and -2 to activate the receptors. Besides the regulatory effects on IGF-1 and -2 functions, IGFBPs exhibit IGF-independent actions, such as growth inhibition and apoptosis.[3]

In normal physiology, IGF-1R stimulates linear body growth, promotes neuronal survival and myelination, postnatal mammary development and lactation, and is implicated in bone formation and renal function.[3] The IGF-1R plays a central role in integrating signals of nutrition and stress into energy shifts from energy-expensive anabolic processes, such as growth and reproduction, to preserving responses under catabolic circumstances[12] (Fig. 3).

In conclusion, the body-wide expression and availability of IGF-1 and IGF-1R and interaction with IR and other signalling pathways are fundamental for its role in the organism. The implication of targeting a receptor that is ubiquitously expressed in normal tissues throughout the body, though, has long been a serious concern.

3. IGF-1R in cancer

The challenge of the last two decades has been to define the exact contribution of IGF-1R to growth and development of a wide range of malignancies and to identify the therapeutic potential of targeting this receptor as anticancer therapy.

The involvement of the IGF-1R in malignant transformation was first recognised in fibroblasts derived from homozygous IGF-1R null mice embryos.[13] Mouse embryo fibroblasts are prone to transformation; however, in the absence of IGF-1R they become resistant to malignant transformation by a number of oncogenes (e.g. Simian Virus 40T antigen (SV40 T), Ewing Sarcoma fusion protein). Re-expression of the IGF-1R restored susceptibility to transformation in these cells.

Animals with homozygous knockout of the IGF-1R die at birth due to poor organ development.[14] Therefore, *in vivo* effects of decreased IGF-1R signalling on tumour growth have been studied in IGF-1 deficient mice. Low IGF-1 levels were associated with reduced growth and metastasis of tumours and xenografts and increased resistance to carcinogen-induced tumourigenesis.[15] Vice versa, transgenic overexpression of IGF-1 in basal epithelial cells induced hyperplasia and well-differentiated adenocarcinomas of skin and prostate.[16,17] In population studies, high serum levels of IGF-1 have been associated with an increased risk on prostate cancer and premenopausal breast cancer.[18] And increased incidence of colorectal adenomas and cancer is seen in acromegaly, in which hypersecretion of GH is accompanied by elevated IGF-1 levels.[19]

In vivo overexpression of IGF-1R accelerated the development of tumours in a mouse model of cancer (RIP1-TAG2).[20] In this mouse model, expression of oncoprotein SV40 T in pancreatic islet β cells leads to tumour formation, which is characteristically accompanied by IGF-2 upregulation, providing an activating ligand for the IGF-1R. Remarkably, IGF-1R overexpressing RIP1-TAG2 mice developed more invasive tumours with an increased amount of distant metastases than parental mice. Recently, transgenic expression of a constitutively active IGF-1R fusion protein in mice resulted in spontaneous development of invasive adenocarcinomas of salivary and mammary glands.[21]

The above-mentioned studies provide proof of principle that active IGF-1R signalling facilitates malignant transformation, drives growth and progression of established tumours and enhances capability to invade and metastasise.

The tumour promoting functions of IGF-1R are embedded in the multi-dimensional process of cancer development and progression. Increased IGF-1R activation, by GH/IGF-1 status or other mechanisms, might create an anti-apoptotic environment thereby favouring cell survival and malignant transformation. Oncogenes, such as the Hepatitis B Virus oncoprotein (HBx) or Ewing Sarcoma fusion proteins, recruit and activate the IGF-1R signalling pathway by increasing transcription of the IGF-1R gene, while loss of tumour suppressor genes, such as p53, BRCA1 or WT1, results in IGF-1R overexpression by loss of transcriptional control.[22] Overexpression of IGF-1R in tumour compared to normal tissue is shown in a number of studies with PCR detection of IGF-1R mRNA.[23,24] Amplification of the IGF-1R gene, however, is infrequent, as shown in breast tumours (<2%)[25,26] and sarcomas.[27] Activating mutations of the receptor have not been described yet. Numerous other molecular mechanisms that modulate IGF-1R signalling in cancer, such as loss of imprinting of IGF-2, altered glycosylation and constitutive activation of downstream proteins, have been described (for a recent review see Ref. 28). Up-regulation of IGF-1R signalling has recently been implicated in the development of resistance to anti-cancer therapy, such as radiotherapy, hormonal therapy and human epidermal growth factor receptor 2 (HER2) targeting.[29,30]

Signalling through hybrid-Rs and IR-A may produce similar tumour promoting effects. Substantiating data from hybrid-R or IR-A knock-out and overexpression models are currently sparse, but IR-A has e.g. been implicated in malignant transformation,[31] autocrine loops with activation by IGF-2[32] and in resistance to gefitinib in colon cancer by overexpression.[33]

Concerns have been raised, therefore, that blocking the IGF-1R might not suffice to abolish all tumour promoting effects of the IGF-1R system.

4. Development of IGF-1R targeting strategies

A number of approaches have been explored to therapeutically interfere in IGF-1R signalling, such as reducing ligand availability by GH antagonists, IGF-1- and IGF-2-antibodies and recombinant human IGFBPs, reducing IGF-1R expression by anti-sense and RNA interference, or inhibiting IGF-1R activation by IGF-1R antibodies and small molecule tyrosine kinase inhibitors (TKIs).[34] *In vitro* and *in vivo* inhibition of IGF-1R signalling in tumour cells resulted in striking apoptosis in malignant cells growing in anchorage independent conditions and dramatic inhibition of tumour formation after injection in nude mice.[35,36]

At present, antibodies and TKIs have become readily available for clinical use. IGF-1R antibodies are currently in phase I and II clinical trials and several IGF-1R TKIs have preclinically been characterised (Table 1).

Binding of IGF-1R antibodies to the receptor prevent ligand-induced activation and induce receptor internalisation and degradation by endocytosis.[51] Receptor downregulation is considered to contribute importantly to the induction of apoptosis seen with IGF-1R antibodies.[35] Preclinical characterisation of IGF-1R antibodies revealed ability to bind and internalise both IGF-1R and hybrid-Rs, while no binding affinity for IR was present.[52,53] For prevention of adverse effects on glucose and carbohydrate metabolism it is desirable to leave IR intact, however, with this approach mitogenic insulin and IGF-2 signalling through the IR-A will be unaffected. Hypothetically, it might prove a functional approach to block auto- and paracrine IGF-2 signalling through the IR-A using IGF-2 antibodies in a subset of tumours that progress due to IR-A signalling. Selective human monoclonal IGF-2 antibodies are currently being developed and characterised.[54] Future studies are needed to clarify the importance of IR-A signalling in tumours.

A recent study suggests that IGF-1R blockage might also lead to a reactive increase in insulin sensitivity.[55] Special attention might, therefore, be needed to prevent hyperinsulinaemia in patients receiving IGF-1R antibodies.

Preliminary results from phase I trials with Pfizer's CP-751,871 and Imclone's A12 show no dose limiting toxicities.[56,57] Infrequently mild transient hyperglycaemia developed, which in some cases was attributable to the combination with steroids. Hypoglycaemia, a potential result from increased insulin sensitivity, has so far not been reported.

Table 1 – Monoclonal antibodies and small molecule tyrosine kinase inhibitors (TKIs) targeted at the IGF-1R in the frontline of early clinical and preclinical development

Compound	Company	Phase of clinical development	Reference
IGF-1R monoclonal antibodies			
CP-751,851	Pfizer	Phase II	37
IMC-A12	Imclone	Phase I	38
H7C10	Merck	Phase I	39
AVE-1642	Immunogen/Sanofi-Aventis	Preclinical	40
R1507	Roche	Preclinical	41
19D12	Schering-Plough	Preclinical	42
AMG 479	Amgen	Preclinical	43
Bispecific antibodies			
Di-diabody IGF-1R/EGFR	Imclone	Preclinical	44
IGF-1R TKI			
PPP	Karolinska Institute/Biovitrum	Preclinical	45
BMS-55417/-536924	Bristol–Myers Squibb	Preclinical	46
NVP-AEW541/-ADW742	Novartis	Preclinical	47,48
Dual inhibitors			
Insm-18: IGF-1R, HER2	Insmed	Phases I and II	49
EXEL-228: IGF-1R, Src	Exelixis	Preclinical	50

IGF-1R antibodies demonstrated *in vitro* activity to numerous solid tumours (breast, lung, colon, cervical, ovarian, pancreatic, melanoma, prostate, neuroblastoma, rhabdomyosarcoma, osteosarcoma) and multiple myeloma (MM).[37,39–43,58,59] *In vivo* tumour regression and growth arrest by IGF-1R antibodies was confirmed in subcutaneous xenografts and metastatic models of breast, colon, lung, pancreas, prostate, ovarian and MM tumours. Monotherapy, as well as combinations of IGF-1R antibodies with chemotherapy, targeted therapy and radiation, such as 5-FU and irinotecan in colon tumour xenografts, gemcitabine for pancreatic tumours, melphalan for multiple myeloma, tamoxifen in breast tumours, anti-EGFR in lung tumours and radiation in lung tumours, were effective and induced 60–100% tumour regressions.[37,39–41,58,60,61]

Early evidence of clinical activity in various solid tumours, hormone refractory prostate cancer and multiple myeloma has been reported.[56,57,62] Interestingly, at doses of 3 mg/kg the IGF-1R expression in peripheral blood mononuclear cells (PBMCs) was completely abrogated, meaning that IGF-1R downregulation in PBMCs could provide a functional bio-marker for adequate dose finding.[56]

TKIs inhibit receptor activation by directly binding to and blocking the catalytic kinase domain. As the kinase domain of IGF-1R and IR are nearly identical, it is hard to achieve specificity for IGF-1R over IR and therefore the chance of undesirable effects of co-targeting the insulin receptor is not hypothetical.[63]

Examples of TKIs with specificity for IGF-1R over IR are Novartis' compounds NVP-AEW541 and -ADW742.[47,48] Bristol–Myer Squibb, on the other hand, has developed TKIs targeting both IGF-1R and IR, BMS-55417 and -536924.[21,46] No data currently exist on the effects of IGF-1R TKIs on hybrid-R signalling.

Interestingly, IGF-1R specific inhibitors, PPP and NVP-AEW541, decreased blood glucose levels in mice, due to increased glucose uptake in IGF-1R positive, but not in IGF-1R negative, cells.[45,64] BMS compounds, on the other hand, induced diabetogenic effects *in vivo*,[46] but addition of metformin reduced hyperglycaemia.[63] The choice of metformin is rational, since metformin reduces hepatic gluconeogenesis and intestinal glucose absorption, while stimulating insulin sensitivity without increasing insulin levels.

In vitro activity of TKIs has been shown in a panel of solid tumours (ovarian, prostate, breast, lung, colon, thyroid, ovarian, renal, adrenal and neuroendocrine tumours, mesothelioma, hepatocellular carcinoma, melanoma, sarcomas and retinoblastoma) and haematological tumours (MM, various subtypes of leukemias and lymphomas). *In vivo* activity of TKIs was demonstrated in animal models of Ewing's Sarcoma, uveal melanoma, prostate cancer, neuroblastoma, fibrosarcoma and MM.[46–48,64–68] Synergistic effects were seen when IGF-1R TKIs were combined with vincristine in Ewing's Sarcoma and melphalan in MM.[47,68]

One broad spectrum TKI with reported activity against the IGF-1R (Insm-18) is currently in phase I clinical trial. This compound inhibits activity of e.g. platelet-derived growth factor receptor (PDGFR) and HER2, as well.[49]

Notably, decreased VEGF production and disturbed angiogenesis has been demonstrated in various models following IGF-1R inhibition.[61,64] Disruption of IGF-1R may be effective against tumour neovascularisation.

5. Potential of IGF-1R targeting in various tumour types

IGF-1R is frequently overexpressed in a wide range of tumour types (Table 2). Although correlations with clinical or pathological parameters are infrequently found, IGF-1R may represent a common target in a spectrum of tumour types, considering the wide range of tumours that are sensitive to IGF-1R blockade by antibodies and TKIs *in vitro* and *in vivo*. Among tumour types and cell lines of same tumour types, however, differential sensitivity to IGF-1R drugs is seen.[40,46,47] No activity of the IGF-1R inhibitor PPP has been shown in

Table 2 – IGF-1R in clinical samples of primary colorectal tumours, prostate tumours, Ewing's Sarcoma (ES), osteosarcoma and multiple myeloma (MM): correlations with tumour grade and survival

Tumour type	Reference	Year	N	Method	IGF-1R overexpression (%)	IGF-1R correlations	
						Grade	Survival
Colon	Cunningham et al.[69]	2006	87	IHC	93	=	=
	Koda et al.[70]	2004	144	IHC	51	=	n.t.
	Nakamura et al.[71]	2004	161	IHC	98	n.t.	↑ RFS
	Peters et al.[72]	2003	713	IHC	99	n.t.	n.t.
	Weber et al.[24]	2002	40	PCR	80	=	n.t.
	Hakam et al.[73]	1999	36	IHC	96	↑	=
	Adenis et al.[74]	1995	20	IGF binding	70	=	n.t.
	Bhatavdekar et al.[75]	1995	59	IGF binding	15	=	=
Prostate	Ryan et al.[76]	2007	31	IHC	77	=	n.t.
	Liao et al.[77]	2005	56	IHC	92	=	n.t.
	Hellawell et al.[78]	2002	39	IHC	95	=	n.t.
ES	Alava et al.[79]	2000	78	IHC	'Most'	n.t.	n.t.
Osteosarcoma	Burrow et al.[80]	1998	46	PCR	46	n.t.	n.t.
	Arihiro and Inai[81]	2001	14	IHC	43	n.t.	n.t.
MM	Bataille et al.[82]	2005	56	FACS	73	n.t.	↓ OS
	Chng et al.[83]	2006	125	PCR	10–20	n.t.	=

Year, year of publication; N, number of patients; IHC, immunohistochemistry; PCR, polymerase chain reaction; IGF binding, radioligand ([^{125}I] IGF-1) binding assay; FACS, fluorescence-activated cell sorting; n.t., not tested; RFS, relapse free survival; OS, overall survival; =, no significant correlation; ↑, positive correlation; ↓, negative correlation.

IGF-1R negative cells,[45] and weaker effects of antibody A12 in a low IGF-1R expressing MM model compared to a high expressing IGF-1R MM model.[61] However, the degree of sensitivity cannot completely be related to IGF-1R expression and, interestingly, MM as a group were more sensitive to the antineoplastic effects of NVP-ADW472 than any other tumour group.[47]

The correlation of IGF-1R expression with clinical and biological parameters is currently most well defined in breast cancer (Table 3). Highly variable percentages (39–93%) of breast carcinomas expressing high levels of IGF-1R are reported, most likely because a uniform method to assess the IGF-1R expression level is lacking. Although controversy still exists,[85,86]

Table 3 – IGF-1R, insulin receptor (IR) and hybrid-R in clinical primary breast cancer samples: correlations with pathological parameters and survival

Reference	Year	N	Method	IGF-1R overexpression (%)	IGF-1R correlations			
					Grade	ER	PgR	Survival
Ueda et al.[84]	2006	150	IHC	47	↓	↑	↑	(ER+) ↑ RFS
Koda et al.[85]	2005	58	IHC	56	=	↓	n.t.	n.t.
Shimizu et al.[86]	2004	210	IHC	43	=	=	=	=
Nielsen et al.[87]	2004	930	IHC	87	n.t.	n.t.	n.t.	=
Schnarr et al.[88]	2000	69	IHC	n.t.	↓	↑	n.t.	n.t.
Happerfield et al.[89]	1997	89	IHC	90	↓	↑	↑	n.t.
Railo et al.[90]	1994	124	IGF binding	39	=	↑	=	(ER–) ↓ RFS
Papa et al.[91]	1993	449	RIA	81	=	↑	=	n.t.
Bonneterre et al.[92]	1990	297	IGF binding	87	↓	↑	↑	↑ RFS ↑ OS
Foekens et al.[93]	1989	214	IGF binding	93	=	↑	=	= RFS = OS
Peyrat et al.[94]	1988	76	IGF binding	93	=	↑	↑	n.t.
					IR correlations			
Matthieu et al.[95]	1997	584	IHC	55	n.t.	n.t.	n.t.	↑ RFS
Papa et al.[96]	1990	159	RIA	'Most'	↑	↑	↑	n.t.
					Hybrid-R correlations			
Pandini et al.[97]	1999	39	ELISA	n.t.	n.t.	=	=	n.t.

Year, year of publication; N, number of patients; IHC, immunohistochemistry; IGF binding, radioligand ([^{125}I] IGF-1) binding assay; RIA, radioimmunoassay; ELISA, enzyme-linked immuno sorbent assay; ER, estrogen receptor; PgR, progesterone receptor; n.t., not tested; RFS, relapse free survival; OS, overall survival; =, no significant correlation; ↑, positive correlation; ↓, negative correlation.

IGF-1R expression in breast cancer is correlated with hormone receptor expression and well differentiated tumours in most studies.[84,88,94] A correlation with prognosis is not consistently demonstrated. Interestingly, Railo et al.[90] found worse survival rates in ER negative IGF-1R expressing tumours, while Ueda et al.[84] recently described a favourable prognosis for IGF-1R expression in ER positive tumours. This observation of a differential effect of IGF-1R expression on prognosis in ER positive versus ER negative tumours is supported by *in vitro* studies. In breast cancer cell lines IGF-1R and ER synergistically stimulate proliferation,[98] but in the absence of ER, IGF-1R activation fails to induce mitogenesis, while its migratory actions are retained.[99,100] It could be hypothesised that well differentiated, ER positive breast cancers retain physiological growth control by ER and IGF-1R signalling, while in ER negative tumours IGF-1R expression confers primarily metastatic capacities.

In prostate cancer, a same close conjunction is seen between IGF-1R and androgen receptor.[101] Interestingly, differential effects of IGF-1R targeting have been demonstrated in androgen dependent versus hormone refractory prostate cancer models *in vivo*.[59] While IGF-1R antibody A12 caused apoptosis and abrogated G1-S phase transition in androgen dependent prostate tumours, IGF-1R inhibition led to G2M arrest in hormone refractory tumours.

Because IGF-1R and hormone receptors closely interact, a combination of hormonal therapy with IGF-1R drugs may be necessary to block all mitogenic hormonal responses and may prevent development of hormone resistance, as modulations of the IGF-1R system have been implicated in development of resistance to endocrine therapies in breast and prostate cancer.[30,101]

In breast cancer cell lines, the IGF-1R has also been shown to interact with and activate the HER2 receptor in cells resistant to anti-HER2 therapy (trastuzumab) and this interaction could be disturbed by lapatinib (a dual EGFR/HER2 TKI) as well as IGF-1R antibodies.[102] This suggests that patients with disease progression on trastuzumab therapy might benefit from IGF-1R antibodies.

In Ewing's Sarcoma IGF-1R expression is a result of the actions of the EWS-ETS fusion proteins, which are fundamental to development of Ewing's Sarcoma. In clinical samples, De Alava et al. demonstrated a relation between a functionally weaker and clinically favourable member of the EWS-ETS family of fusion proteins, EWS-FL1 type 1, a lower proliferative rate and lower levels of IGF-1R expression.[79] As the EWS-ETS fusion proteins are transcription factors, whose function cannot easily be blocked, it is promising that it may soon become possible and prove effective to block its targets, among which the IGF-1R. Blocking the IGF-1R has demonstrated *in vivo* effects in Ewing's sarcoma by several approaches.[64,68,103,104]

6. Concluding remarks

Although responses to IGF-1R drugs are anticipated in a wide range of tumours based on *in vitro* and *in vivo* results, the clinical and biological correlates of IGF-1R response in tumours are poorly understood. Considering previous experiences with RTK targeting drugs, the concept that IGF-1R drugs will be widely applicable in anticancer therapy due to ubiquitous expression of IGF-1R in tumours might prove not to be true. Biomarkers are urgently needed to predict responses and select patients who may benefit from IGF-1R targeted therapy.

Further dissection of the mechanistic basis of IGF-1R and IR function could improve specificity and efficiency of IGF-1R targeting within the context of a highly versatile receptor system. Such knowledge should translate into strategies which block tumour promoting elements of the IGF-1R/IR-system and avoid hitting vital metabolic functions. In this respect, the role of signalling via IR-A signalling and downstream proteins, such as IRS-1 and -2, is emerging. Also, joint efforts of oncologists and endocrinologists might manage issues related to diabetogenic side effects and compensatory mechanisms resulting from IGF-1R targeted therapy, such as increased insulin sensitivity and increases in glucose uptake. With upcoming clinical trials much of the issues covered in this review might be resolved in the coming years.

Conflict of interest statement

None declared.

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