

The role of insulin and IGF system in pancreatic cancer

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Abstract

The importance of the IGF system in carcinogenesis has been established for many solid cancers. It is well known that individuals with higher circulating levels of the IGF1 ligand present an increased risk of cancer. However, therapies with monoclonal antibodies targeting the IGF1 receptor (IGF1R) have been largely unsuccessful. One of the potential reasons for this failure is the existence of the highly homologous insulin receptor (IR), which appears to be at least equally efficient as the IGF1R in the transition of mitogenic signals to the nucleus and promotion of cell growth. Furthermore, IGF1 and insulin receptors can form hybrid receptors sensitive to stimulation of all three ligands of the system: insulin, IGF1, and IGF2. Although the connection between insulin, diabetes, and cancer has been established for years now, clear evidence that demonstrate the redundancy of insulin and insulin receptors and insulin-like growth factors and their receptors in cancer is missing. In this review, we focus on the contribution of insulin and IGFs to carcinogenesis in the insulin-producing organ, the pancreas. We give a short summary on the complexity of insulin and the IGF system in the pancreas and their potential roles in pancreatic cancer, especially pancreatic ductal adenocarcinoma. Finally, we discuss drug-targeting options of this system and the rationale of simultaneous targeting of both the insulin and the IGF systems.

Key Words

- ▶ Insulin
- ▶ Insulin-like Growth Factor
- ▶ pancreatic cancer

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The human pancreas is a complex exocrine and endocrine gland with two vital functions: production of digestive juices and regulation of glucose metabolism. Its complexity is also reflected in the fact that three different types of tumors can develop in the pancreas, two in the exocrine and one in the endocrine part of the gland. Pancreatic ductal adenocarcinoma (PDAC) and acinar cell carcinoma develop in the exocrine pancreas. Most exocrine cancers are PDAC while acinar cell carcinomas are very uncommon. Neuroendocrine tumors develop in the endocrine pancreas and are generally rare.

PDAC is a devastating disease and is the fourth leading cause of malignancy-related death in humans (Hidalgo 2010). Though of low incidence, late detection and lack of effective chemotherapies make this cancer one of the deadliest, with a 5-year overall survival rate lower than 5% (Li *et al.* 2004, Jemal *et al.* 2008). In the last decade, substantial research efforts in investigating pancreatic carcinogenesis have broadened our knowledge and many molecular mechanisms essential for PDAC carcinogenesis and its maintenance have been described (Hingorani *et al.* 2005, Siveke & Schmid 2005, Izeradjene *et al.* 2007, Mazur & Siveke 2012). Still, efficient therapies are missing and targeted approaches have been largely disappointing. Are we missing something?

The insulin-like growth factors (IGF1 and IGF2) and their receptors (IGF1R and IGF2R) have been acknowledged as important players in a variety of cancers. The connection between circulating IGF1 levels and the risk of cancer has already been demonstrated (Emerman *et al.* 1985, Chan *et al.* 1998, Hankinson *et al.* 1998). IGF1R is a tyrosine kinase that activates intracellular signaling cascades responsible for cell survival and proliferation, implicating that deregulation of such signaling might lead to non-regulated cell growth and cancer (Yakar *et al.* 2004, Samani *et al.* 2007, Belfiore *et al.* 2009, Massoner *et al.* 2010). Interestingly, IGF1R has been found to be over-expressed in many cancers and is thus very appealing as a druggable target (Pollak 2008a, Gallagher & LeRoith 2011). Despite initial enthusiasm, a considerable number of clinical trials with antibodies targeting IGF1R in many different cancers have failed as no significant clinical improvement was observed upon blocking of IGF1R (Yee 2012). In this review, we will try to summarize the current knowledge on the IGF and insulin networks and their role in PDAC and offer some provocative solutions for the future of therapeutic targeting of these systems in PDAC.

The IGF system in PDAC

In physiological conditions, IGFs are peptides synthesized mainly by the liver and are major stimulators of tissue and cellular growth (Pollak 2008b). In general, IGFs stimulate proliferation and inhibit apoptosis in target tissues (Yu & Rohan 2000). In rodents, mouse knockout studies substantiated that IGF2 is more important for early fetal development and IGF1 is necessary for achieving maximal growth, while in humans, both IGF1 and IGF2 are expressed in adulthood (DeChiara *et al.* 1990, Ohlsson *et al.* 2009, Yakar & Adamo 2012). Additionally, it is generally accepted that IGF1 signaling through IGF1R is responsible for cell growth-regulating actions (Yu & Rohan 2000), while IGF2R does not seem to activate intracellular signaling pathways and works rather as a scavenger receptor for IGF2.

Evidence suggests that the IGF system is intimately involved in development and progression of pancreatic cancer. In PDAC patients, studies have reported on increased intratumoral expression of IGF1R (Hakam *et al.* 2003) and this has been associated with higher tumor grade and poor survival (Valsecchi *et al.* 2012). Furthermore, increased amounts of IGF1 and IGF-binding proteins have been detected in sera and tissues of PDAC patients (Korc 1998, Karna *et al.* 2002). Dong *et al.* (2010, 2012) analyzed single nucleotide polymorphisms among

the members of the IGF axis in humans and found significant associations between IGF axis gene variants and haplotypes and risk as well as clinical outcome in PDAC patients. *In vitro* experiments showed that exogenously added IGF1 increases the growth of PDAC cancer cell lines (Bergmann *et al.* 1995, Yao *et al.* 2002) and this effect can be blocked by an IGF1R-specific antibody (Bergmann *et al.* 1995). IGF1R exerts antiapoptotic effects and plays a role in proliferation and motility of cancer cells (Liu *et al.* 2008, Tomizawa *et al.* 2010) supporting the mitogenic and metastatic role of this molecule.

Although the data suggest that the IGF system might be important for PDAC, clinical trials performed with IGF1R blocking antibodies were largely disappointing (Rieder *et al.* 2011). Very recently, Amgen (2012) announced the termination of a large Phase III clinical trial in patients with metastatic PDAC treated with the IGF1R-blocking antibody ganitumab (AMG 479) in combination with standard of care chemotherapy gemcitabine due to no significant improvement in the overall survival of the patients.

IGF and insulin receptors as tyrosine kinases in PDAC

One of the potential reasons for failure of IGF1R-targeted therapies is the coexistence of a structurally and functionally related insulin receptor (IR) in cancers. Two IRs exist: IR-B, which is responsible for metabolic actions of insulin and is expressed on metabolically active tissues, and IR-A, which is usually found in fetal tissues and, interestingly, reappears in cancer (Frasca *et al.* 1999). IRs and IGF1Rs are members of the same family of transmembrane receptor tyrosine kinases. They have evolved from a common parental family member, and, in primitive organisms, insulin-like signaling regulates cell proliferation and survival (Garofalo 2002, Barbieri *et al.* 2003, De Meyts 2004). Both IGF1Rs and IRs are expressed on the cell surface, as holoreceptors comprised of two extracellular α -subunits, ligand binding domains, and two transmembrane tyrosine kinase β -subunits. A high degree of homology is reflected especially in their tyrosine kinase domains, which share up to 85% of similarity in amino acids (Malaguarnera & Belfiore 2011). Once their ligands are bound, the receptor tyrosine kinase domains of the holoreceptors are autophosphorylated and further promote phosphorylation and activation of IR substrate 1 (IRS1) and the SHC1 protein to initiate downstream signaling cascades. The actions of both IRs and IGF1Rs are mainly performed via two major signaling cascades: MAPK

and phosphoinositide-3-kinase (PI3K; Vivanco & Sawyers 2002, Gallagher & LeRoith 2011, Siddle 2011). A representation of the receptors and activated signaling pathways in the pancreas and in PDAC is given in Fig. 1. MAPK pathway activation mainly results in proliferation while PI3K activation results in glucose uptake regulation, inhibition of apoptosis, and stimulation of protein synthesis (Belfiore *et al.* 2009, Godsland 2010). In the case of PDAC, both PI3K and MAPK signaling pathways have been suggested to be central signaling cascades (Appleman *et al.* 2012, Neuzillet *et al.* 2012). KRAS, one of the RAS proteins, is mutated in >90% of PDAC cases (Almoguera *et al.* 1988) and it is well established from human and mouse studies that mutation in the *Kras* gene is one of the first oncogenic insults in the pancreas sufficient to initiate cancer development (Hingorani *et al.* 2003). In very recent work, Appleman *et al.* (2012) demonstrated the direct connection between IGF1R, MAPK, and PI3K signaling in pancreatic cancer. Namely, the authors demonstrated that mutated *KRAS* and downstream MAPK signaling as well as autocrine activation of IGF1R by IGF2 ligand are necessary for activation of PI3K signaling and proliferation of pancreatic ductal epithelial cells. It was also shown that even in the presence of

mutated *KRAS*, epithelial cells require functional IGF1R for development of PDAC and that only combined inactivation of both IGF1R and MAPK reduced survival of pancreatic ductal epithelial cells. Tanno *et al.* (2001) demonstrated that active AKT induces expression of IGF1R in the pancreatic cancer cell lines PANC1 and AspC1 and inhibition of AKT signaling leads to a decrease in IGF1R expression. They suggested that this relationship between IGF1R and AKT is one of the mechanisms that promotes invasiveness of pancreatic cancer.

In normal, healthy tissues, the functions of IGF1R and IR receptors are rather distinct with IRs being more responsible for glucose metabolism and IGF1R for cell growth and proliferation (Belfiore *et al.* 2009). In a changed state, for example the tumor, receptors might lose these signaling distinctions and could start performing very similar actions. In human PDAC cancer cell lines, increased expression and mitogenic signaling via high-affinity IR-A has been reported (Fisher *et al.* 1996). This change in ratio of IR expression in favor of IR-A has been reported in cancers and is thought to profoundly influence the cellular response to insulin and IGFs. In addition to insulin, IR-A also binds the IGF2 ligand and exposes the cell to the strong growth-promoting effects of IGFs (Frasca *et al.* 1999). Recent work in a mouse model of pancreatic neuroendocrine cancer showed that IR indeed possesses functional redundancy with IGF1R, can be stimulated by IGF2, and can take over the cancer-promoting role of IGF1R, thus conveying resistance to IGF1R-targeted therapies (Ulanet *et al.* 2010). Notably, the authors demonstrated that IR expression gradually increases from the stage of hyperplastic lesions to tumor. Genetic ablation of IR led to impairment of tumor progression and sensitization of islet tumors to IGF1R-targeted therapies, suggesting that IR contributes at least as equally as IGF1R in cancer signaling functions of IGF2.

Furthermore, an emerging issue in human cancers is existence of hybrid IGF1R:IR receptors (Pandini *et al.* 1999, 2002, Vella *et al.* 2001, Malaguarnera & Belfiore 2011). Hybrid receptors, especially the INSR-A:IGF1R, have a high affinity toward IGF2 as a ligand and thus dramatically increase the responsiveness of cells to IGF2 mitogenic signaling (Belfiore *et al.* 2009). An overview of receptors, their ligands, and binding affinities is given in Fig. 2.

Insulin in PDAC

Though the existence of hybrid receptors and their function in many cancers, including PDAC, is a matter of debate, increasing evidence support that insulin

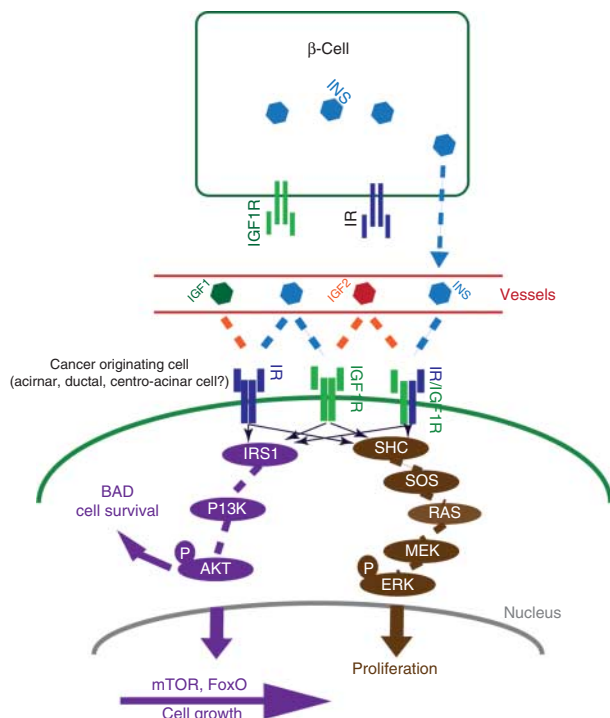
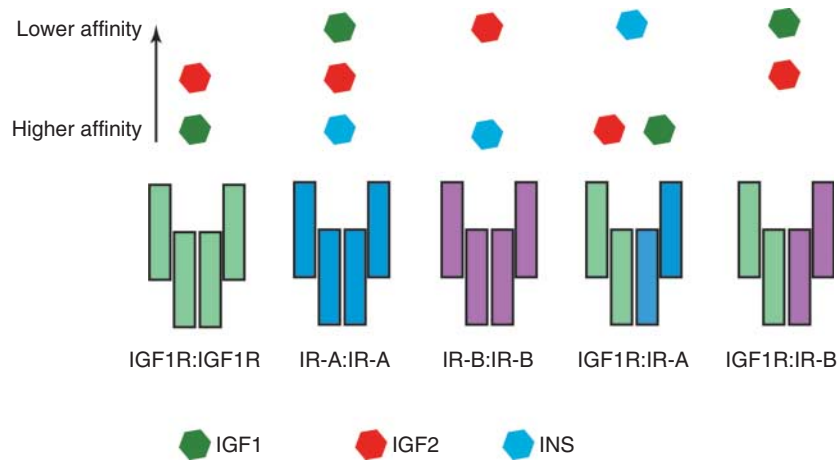


Figure 1
Signaling cascades of insulin and IGF in the pancreas and in pancreatic cancer.

**Figure 2**

Insulin and IGF homodimeric and hybrid receptors and their ligands.

potentially plays a parallel role to the IGF system in PDAC and is at least equally as important in cancer-promoting actions as the IGF system. Insulin is produced by β cells in the Langerhans islets of the pancreas, is secreted into the blood, and regulates cellular glucose uptake as well as the uptake of amino and fatty acids. This function of insulin is initiated by binding of an insulin molecule to its prospective receptor on the cell surface resulting in intracellular signaling and membrane expression of glucose transporters. Glucose molecules are then transported into the cell and used for catabolic or anabolic processes, with decreasing blood glucose levels being one major effect. IR-B is expressed in the insulin-secreting organ, the pancreas itself, and, even more importantly, is involved in the autocrine regulation of insulin secretion. Early mouse studies demonstrated that a β -cell-specific *IR* knockout leads to development of progressive glucose intolerance, smaller islets, and decreased insulin content as well as a delay in acute insulin secretion from the islets (Kulkarni *et al.* 1999). Insulin, however, not only regulates glucose homeostasis in the body but also acts as a growth-promoting factor and as such can contribute to carcinogenesis in many cancers including PDAC (Godsland 2010, Bao *et al.* 2011, Cui & Andersen 2012). Of note, diabetes mellitus (DM) patients, typically type 2 DM (T2DM) patients, have an increased risk of PDAC. A new onset of DM is a phenomenon exclusively related to PDAC among a few of the investigated cancers (Ben *et al.* 2011, Aggarwal *et al.* 2012). Moreover, DM patients on insulin substitution are at higher risk of developing PDAC than those receiving metformin as an antidiabetic drug (Li *et al.* 2009, Grouven *et al.* 2010). Now, why is this the case? T2DM, occurring in

95% of adult DM cases, is characterized by peripheral insulin resistance and compensatory hyperinsulinemia (Reaven 1995, Gapstur *et al.* 2000). There is clear evidence that high insulin levels increase the risk of cancer by activating mitogenic signals on cells (McCarty 2001, Belfiore *et al.* 2009, Malaguarnera & Belfiore 2011). Many potential actions of the insulin system in PDAC have been reported. In humans with T2DM, an increase in ductal replication rate that precedes PDAC has been reported (Butler *et al.* 2010). An overexpression of docking peptides that intracellularly transmit the activation of IR, IRS1 and IRS2, and consequent overactivation of the PI3K signaling cascade has been observed in human PDAC tissues and cell lines (Bergmann *et al.* 1996, Kornmann *et al.* 1998, Asano *et al.* 2005). It has also been shown that IR shows cross talk with G-protein-coupled receptors and further activates mTOR signaling and stimulates DNA synthesis and proliferation of cancer cells in PDAC (Rozengurt *et al.* 2010). Also, PDAC cancer cells kept in culture increase their proliferation rate in direct response to the addition of insulin into the medium (Fisher *et al.* 1996).

How do IGF and the insulin systems cooperate and collaborate in PDAC?

PDAC develops from the exocrine part of the pancreas, yet the cell of origin is still not known (Hezel *et al.* 2006). In fact, there is evidence that multiple different cell types in all pancreatic compartments may serve as cancer-originating cells (Bardeesy & DePinho 2002). Evidence from genetically engineered mouse models supports the view that acinar cells suffer the oncogenic insult and go

through the process of acinar to ductal metaplasia followed by malignant transformation (Hezel *et al.* 2006, Mazur & Siveke 2012). Exocrine cells are in the vicinity of the islets of Langerhans and are thus directly exposed to high insulin concentrations. A complex 'insulo-acinar portal system' (Williams & Goldfine 1985) supplies the exocrine part of the pancreas with blood coming from the islets and is thus rich in insulin but also in glucagon, somatostatin, and other molecules secreted by the endocrine pancreas. This implies that functions of the exocrine pancreas may be regulated by the hormones of the endocrine pancreas (Barreto *et al.* 2010). Evidence suggests that insulin regulates both growth and function of the exocrine pancreas. It is known that diabetic patients under insulin therapy suffer from impairment of the exocrine pancreatic function (Lankisch *et al.* 1982). In rats and mice, it has been demonstrated that insulin regulates amylase secretion (Barreto *et al.* 2010) via IRs expressed on the acinar cells (Mossner *et al.* 1984, Okabayashi *et al.* 1989). Taken together, exposure of the exocrine pancreas to higher insulin concentrations as well as the presence of the receptor tyrosine kinases IR and IGF1R in the exocrine pancreas might lead to the idea that exocrine cells are exposed to a high mitogenic challenge that can be of crucial importance for cancer development and its progression. Indeed, only lately, the role of receptor tyrosine kinase receptors in PDAC carcinogenesis has been emphasized, and approaches using genetically engineered mice showed that receptor activation upstream of mutant KRAS is necessary to provide a permissive environment for KRAS transforming actions (Ardito *et al.* 2012, Navas *et al.* 2012). Pancreas-specific ablation of epidermal growth factor receptor (EGFR) with concomitant activation of oncogenic KRAS blocked development of PDAC, suggesting that EGFR-dependent signaling is necessary to allow initiation of PDAC development through the RAS/RAF/MEK/ERK cascade. IR and IGF1R belong to the same family as EGFR and trigger similar cascades. Analysis of human PDAC samples showed existence of a potential cross talk of IGF1R with EGFR that may be relevant for progression and metastasis of cancer and to predict patient outcome (Ueda *et al.* 2006, Valsecchi *et al.* 2012). In this regard, the cellular localization of both receptors seems to be important, as especially the membrane-dominant IGF1R and the cytoplasmic-dominant EGFR expression was related to poor survival and higher tumor grade (Ueda *et al.* 2006).

Overall, it seems that IGF1R/IR overexpression and activation in PDAC might be of central importance and a potentially good therapeutical target. One of the obvious

tasks for the future is to investigate whether functional IGF1R and IR are more important for PDAC initiation or maintenance of already established cancer. Thus, generation and characterization of suitable mouse models where parts of the IGF/insulin signaling network are genetically removed specifically in the pancreas might help us to better understand their role in pancreatic cancer development and progression as well as create new hypotheses about potential therapeutic targeting of these apparently crucial signaling systems.

IR- and IGF1R-targeted therapies in the treatment of PDAC

Three different strategies are applied for blocking IGF/insulin signaling in cancers: receptor blockade via MABs, kinase inhibition with small molecular inhibitors, and ligand sequestration. There are many problems along the way to successful therapeutic targeting of insulin and IGF system in cancers. Especially, targeting IR can potentially cause hyperglycemia and adverse metabolic effects (Weroha & Haluska 2008). Another issue is that, due to the high structural and functional homology of IGF1R and IR, if one is blocked, the other receptor may redundantly take over the function as a resistance mechanism (Malaguarnera & Belfiore 2011). Even more, the expression of non-targeted receptors might even increase. Furthermore, if hybrid IGF1R:IR-A receptors are the dominating species in cancer, specific blocking of only IGF1R or INSR would be of limited benefit as the hybrid receptor is not targeted and will continue signaling.

Clinical trials of IGF1R blocking antibodies on PDAC patients were recently either terminated without success (Amgen 2012) or are still ongoing (www.clinicaltrials.gov; IMC-A12 and MK0646). Boehringer-Ingelheim has recently launched a Phase I clinical trial for the treatment of solid tumors, including PDAC, with the IGF-neutralizing antibody BI836845 (www.clinicaltrials.gov). In comparison to IGF1R-blocking antibodies, a potential appeal of this strategy lies in the fact that BI836845 shows high affinity toward the ligands IGF1 and IGF2 but not insulin and should not only decrease the signaling of IGF1R homodimers but also of the hybrid receptors and IR-A in cancer. It would allow normal function of the metabolic regulator IR-B and blocking of proliferative signaling from IGF1 and IGF2 with any of their receptors.

Concluding remarks

The aggressiveness of PDAC is mirrored in the complexity and redundancy of the molecular pathways activated during the carcinogenic and metastatic process. It is to be doubted that even a successful targeting of IR/IGF1R will be a magic bullet in PDAC therapy. Increasing evidence supports the contribution of insulin to pancreatic carcinogenesis. Insulin seems to be more significant than thought so far and should be considered with more attention. Further detailed work will be needed to define the clinical scenario, state of disease, and potential subgroups that may benefit from IGF1R/IR targeting. Suitable and sophisticated research approaches and identification of those disturbances that convert important metabolic regulators to malicious cancer-promoting molecules remain a central task to the scientific field.

Declaration of interest

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

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