Review

Nuclear Receptors in Pancreatic Tumor Cells

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Abstract. *Aim: This review focuses on nuclear receptors expressed in pancreatic cancer. Materials and Methods: An extensive search of articles published up to March 2013 was conducted using the MEDLINE database. The key words used were "pancreatic cancer", "molecular receptors" and "growth factors". A total of 112 articles referred to pancreatic cancer, molecular receptors and/or growth factors were included. Results: Receptors of growth factors, such as the epithelial growth factor receptor, insulin-like growth factor-1 receptor, vascular endothelial growth factor receptor and others, such as integrin α5β1, somatostatin receptors, the death receptor 5, claudin, notch receptors, mesothelin receptors, follicle-stimulating hormone receptors, the MUC1 receptor, the adrenomedullin receptor, the farnesoid X receptor, the transferrin receptor, sigma-2 receptors, the chemokine receptor CXCR4, the urokinase plasminogen activator receptor, the ephrine A2 receptor, the GRIA3 receptor, the RON receptor and the angiotensin II receptor AT-1 are expressed in pancreatic tumor cells. These molecules are implicated in tumor growth, apoptosis, angiogenesis, metastasis etc. Conclusion: After identifying the molecular receptors associated with the pancreatic cancer, many more target molecules playing important roles in tumor pathophysiology and senescence-associated signal transduction in cancer cells will be identified. This may have a significant influence on diagnosis, therapy and prognosis of pancreatic cancer.*

In developed countries, among the major causes of cancer deaths, pancreatic cancer (PC) holds the fourth position and the tenth worldwide (1-5). With only 6% of overall rate of 5-year survival and 6 months median survival, PC is among the most devastating human malignancies (1, 6, 7). Fortunately, its incidence is low. Out of all cancers, PC represents 3% and holds the tenth position among the most common causes of cancer and cancer deaths in the USA with similar incidence (3.9%) worldwide (1, 4).

The most important risk factor of PC is smoking, as it is responsible for approximately 25% of all cases (8). Family history is also an important risk factor, accounting for 10% of all PC cases (9-11). PC is strongly associated with increasing age (>55 years) having the higher median age at diagnosis (72 years) and is more likely to occur in men than in women (12). Other risk factors include obesity, lack of exercise, chronic pancreatitis (probably) and type II diabetes (13-15). Given the ageing of the population and the increasing appearance of some of the lifestyle risk factors (obesity, smoking) an increasing prevalence and mortality for PC is expected (2, 8, 16, 17).

The prognosis of PC is bad since it is often diagnosed late and is no longer surgically resectable. Often, during the process of diagnosis, metastases already exist (15, 18, 19). Many reports indicate that perineural invasion is one of the determinants of local recurrence and poor prognostic factors. The molecular basis behind the perineural invasion of such tendency is majorly not known. Once local recurrence has started or metastases have grown, PC is highly resistant to any therapeutic regimen examined until now. Only a poor clinical response (23.8%) to palliative treatment with gemcitabine has been observed (7, 20, 21). The absence of options for effective treatment for PC asks for novel targets and novel therapies including gene therapy (18, 19).

This leads to the identification of biomarkers on an urgent basis, which may contribute to the detection of PC at an earlier stage and to understand the detailed mechanisms of the disease in a better way assisting, thus, to the development of effective strategies towards prevention and treatment. Current data suggest a large number of biomarkers. It seems that 14-3-3σ, S100P, S100A6 and 4-integrin are the most

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Key Words: Pancreatic cancer, nuclear receptors, growth factors, tumor cells.

prominent biomarkers for PC; molecules that are highly and specifically expressed in PC and belong to the S100 protein family, basically S100A6, S100A11 and S100P, as well as S100P and S100A11 (22, 23). These markers are tumor receptors that are specifically over-expressed in pancreatic tumor cells. We, herein, present the role of these receptors in PC and their clinical implications (Table I).

Materials and Methods

A search for articles published up to March 2013 was conducted using the MEDLINE database. The important key words used for searching were "pancreatic cancer", "molecular receptors" and "growth factors". We found 112 articles referred to PC and molecular receptors and/or growth factors, which we included in this review.

Results

Characteristic Receptors of Pancreatic Tumor Cells

Receptors of growth factors. Previous reports have shown the over-expression of members of the epidermal growth factor (EGF) family, fibroblast growth factor (FGF) family, transforming growth factor-beta family (TGF), platelet-derived growth factor family (PDGF), nerve growth factor family (NGF), insulin-like growth factor family (IGF) and their signaling receptors in chronic pancreatitis and PC. In chronic pancreatitis, the over-expression of growth factors and their receptors contributes to tissue remodeling and fibrogenesis. In contrast to chronic pancreatitis, PC is associated with a variety of genetic alterations, including mutations in tumor suppressor genes and cell-cycle regulators, such as p53, c-Myc and K-ras. Cell proliferation is the result of the modification in the expression of growth factors and their receptors, which promotes tumorogenesis and metastasis (24).

Ras, which is a 21-kDa membrane-bound GTP-binding protein, plays a vital role in growth factor-mediated signal transduction pathways. The protein of a GTP is locked in a bound condition by a collectively activated form of Ras, which is the outcome of mutations and this protein has the potential of initiating a multitude of downstream signaling cascades. Farnesylation of the C terminus, by farnesyl protein transferase, is responsible for post-translational enhancement of the Rasprotein. Though in stage III trials farnesyltransferase inhibitors were unsuccessful, yet this intervention is considered to be an important therapeutic target (25-27). In the form of RNA interference, alternatives targeting directly at K-Ras proteins are already present, (28) as well as in association with radiation (29). The FDA has approved the use of sorafenib, which is an inhibitor of Raf-1 kinase and of the vascular endothelial growth factor receptor-2 in order to treat renal cell carcinoma (30). In spite of toleration by the patient, it is inactive in patients suffering from advanced PC (31).

On the other hand, cetuximab is a chimeric monoclonal antibody that binds to the extracellular domain of EGFR, promoting the receptor's internalization and subsequent degradation without any receptor phosphorylation, chemical alteration and, therefore, activation. This fact diminishes the available receptor for natural ligand binding and prevents any further activation of EGFR-associated receptors (32). The first clinical trial in patients with advanced PC was tested with cetuximab and gemcitabine, which showed an encouraging 1-year survival rate of 32% in a phase II trial and has led to the SWOG S0502 phase III trial (33).

Furthermore, erlotinib is an orally active drug that binds the ATP binding site on the intracellular kinase domain, therefore preventing the activity of tyrosine kinase. Patients suffering from advanced PC participated in a phase III trial consisting of 569 patients, examining erlotinib mixed with gemcitabine (34). With a median survival of 6.4 *vs*. 5.9 months (p=0.025) and an 1-year survival of 24% *vs*. 17%, respectively, the overall survival was significantly better in the erlotinib team in comparison to the placebo arm. The use of this drug has been limited though, since most patients developed a distinctive rash. In 2005, the FDA gave approval to erlotinib; however, European registration has been given only to patients suffering from metastatic disease and not to patients detected with locally advanced cancer.

An anti-VEGF monoclonal antibody called bevacizumab was found to have a minor effect in combination with gemcitabine in advanced PC (35). The trial of Avita, which included treatment with gemcitabine and erlotinibin conjunction with or without bevacizumab has been stopped. For the treatment of PC, multi-targeted tyrosine kinase inhibitors like- ZD6474, which is a dual EGFR and VEGF receptor-2, a small-molecule tyrosine kinase inhibitor and sunitinib, a VEGF receptor 1, 2 and 3, c-KIT and PDGF receptor a and b tyrosine kinase inhibitor, hold some promise (36, 37).

EGF receptor. The EGF receptor belongs to a large family of cell surface receptors comprising of 4 isotypes EGFR/ErbB, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4. Bonded by ligands, EGFRs are dimerized and induce activation of Ras-MAPK and PLC-γ pathways. Signal transduction from extracellular stimuli to the nuclear level is controlled and regulated by the proto-oncogene *HER-2/neu* or *ERBB2* with its protein HER-2/neu. Their rate of amplification or over-expression in PC ranges between 16 and 65% in earlier studies (17). The uncontrolled proliferation of cancer cells can result from the over-expression of these molecules (38). A 42% HER-2-positive staining and 16% *HER-2* gene amplification in PC tissue samples were shown by a latest report conducted by improved techniques (39, 40). The EGFR signal transduction pathway is essential for tissue and organ

Table I. *Receptors with high expression in PC cells, their role in PC and clinical implications*.

Receptor	Receptor type	Role in PC	Clinical implications
EGF-R	Growth factor cell surface receptors	Oncogenesis, Angiogenesis, Liver Metastasis	Therapy: Inhibition of tumor angiogenesis & metastasis
IGF-1R	Growth factor tyrosine kinase receptors	Angiogenesis, Liver Metastasis	Therapy: Inhibition of tumor growth *via* IGF-1R
VEGF-R	Growth factor tyrosine kinase receptors	Lymph node metastasis, lymphatic & venous invasion	Therapy: Enforcement of immune memory against proliferating cancer cells
Integrin-α5β1	Heterodimeric transmembrane receptors	Angiogenesis	Therapy: Inhibition of tumor growth
Somatostatin receptors	G protein-coupled receptors	Over-expressed in adjacent to PC normal sites	Therapy: Induce overexpression of serotonin receptors
DR5	Trimeric transmembrane receptors of the TNFR superfamily	Selectivep53-independent apoptosis only of cancer cells	Therapy: Activation of the DR5 enhances antitumor activity of chemotherapeutic drugs
Claudin	Proteins of tight junctions	Receptor of the CPE food poisoning. CPE is toxic for PC expressing Claudin4	Therapy: CPE reduces the growth of the tumor
Notch receptors	Cell surface receptors	Vascularization of the tumor	Therapy: Down-regulation of the notch pathway reduces proliferation of tumor cells, increases apoptosis and decreases invasion
Mesothelin receptor	Anchored cell surface protein	Over-expression only in PC cells and not in normal cells	Diagnosis/Therapy: Unique tissue distribution pattern
FSH receptor	Transmembrane G-protein-coupled receptor	Over-expression in blood vessels of near tissues adjacent to tumor	Early cancer detection/Therapy: Imaging techniques in combination to anti-FSHR antibodies could make PC visible at earlier stages.
MUC1 receptor	Type I membrane glycosylated protein	PC cell survival and proliferation	Therapy: Targeting MUC1R expressing PC; may inhibit tumor growth
ADM receptor	Cell surface receptor	PC growth and metastasis	Therapy: Control of tumor growth and metastasis
Farnesoid X receptor	Ligand-dependent nuclear receptor heterodimer with retinoid X receptor	PC growth and metastasis	Therapy: Inhibition of tumor proliferation, migration, invasion
Transferrin receptor	Membrane-bound protein	Over-expressed in PC but not in normal pancreas tissue	Diagnosis/Therapy: Marker of malignant transformation the pancreas
Sigma-2 receptors	Sigma receptor class	Apoptosis and chemotherapy sensitization	Therapy: Activation of this receptor induces PC cell apoptosis
Chemokine receptor CXCR4		PC invasion and metastasis	Early stage Therapy: Target for chemoprevention and early stage therapy
uPAR	Cellular receptor	PC migration and invasion	Therapy: Direct inhibition of uPAR leads to decreased growth of PC
EphA2 receptor	Tyrosine kinase receptor family	Tumor growth, metastasis	Therapy: Targeting EphA2 expressing PC may inhibit tumor growth and metastasis
GRIA3 receptor	Subunit of ionotropic glutamate receptors	Tumor cell survival, proliferation and migration	Therapy: Targeting GRIA3 may inhibit PC proliferation, survival and migration
RON receptor	Tyrosine kinase	Migration, invasion and apoptotic resistance of PC cells	Therapy: Reduction in the PC growth
AT-1 receptor	G-protein-coupled receptor	PC angiogenesis	Therapy: Blocking of the AT1R might prevent metastasis and prolong survival
NR4A receptors	Nuclear receptor	Controls survival and death of PC cells Over-expressed in PC	Therapy: Inhibition of PC growth pro-apoptotic agents inducing NR4A
PPAR	Steroid receptor superfamily, ligand-activated nuclear receptors	PPARγ isotype is highly expressed in PC. Involved in PC pathogenesis	Prognosis/Therapy: Activation of PPARγ pathway inhibits PC growth
ER	Nuclear ligand inducible transcriptional receptor	Over-expressed in PC with not clear role	Prognosis/Therapy: The ratio ER-β/ER-α may predict response to estrogen-related therapy

ADM, Adrenomedullin; AT1, angiotensin II receptor 1; CPE, C. perfringens enterotoxin; CXCR4, chemokine (C-X-C motif) receptor 4; DR5, death receptor 5; EGFR, epidermal growth factor; EphA2,ephrin type-A receptor 2; ER, estrogen receptor; FSH, follicle stimulating hormone receptor; GRIA3, glutamate receptor ionotropic AMPA receptor; IGF-1R, insulin-like growth factor receptor 1; MUC1,mucin 1 cell surface associated receptor 1; NR4A, nuclear receptor 4A; PPAR, peroxisome proliferator-activated receptor; RON, macrophage-stimulating protein receptor; Upar, urokinase plasminogen activator receptor; VEGFR, vascular endothelial growth factor receptor.

differentiation and regulation of cell migration, adhesion and proliferation. In many cancers, including PC, activated EGFR has been found in association with many pathophysiological mechanisms that include oncogenesis, angiogenesis, apoptosis, inhibition and tumor metastasis (41). In PC, EGFR over-expression is associated with an advanced disease stage, which suggests a putative role of the EGF pathway in the progression of PC (42).

For the oncogenesis of PC it has been suggested that a synergistic action between EGFR and HER-2/neu may lead fibroblasts to malignant state (43). Additionally, the over-expression of EGFR and its ligands leads to an autocrine loop that continuously stimulates cancer cell proliferation, resulting in increasing tumor size, aggressive disease and poor prognosis (41, 44-46). Tumor angiogenesis is mediated through the EGFR/TGF-α activation of the VEGF pathway (47). EGFR over-expression is also associated with PC metastasis to liver (48).

A phenotypically different and quite rare population of CD44 and CD24 epithelial-specific antigen $(ESA)^+$-expression tumor-initiating cells (TIC) was reported by Al-Hajj *et al*. (49) in 2003. The neural stem cell antigen CD133, being expressed in brain-derived TICs from pediatric medulloblastomas and astrocytomas, was demonstrated by Singh *et al*. (50). $CD133^+$ subpopulations from these tumors could initiate *in vitro* neurospheres that showed self-renewal, differentiation and proliferative characteristics similar to normal brain stem cells (50, 51). Also, transplantation of $CD133^+$, but not CD133 cells into NOD/SCID mice, was sufficient to induce growth of tumors *in vivo* (52). These cells are called cancer stem cells, similar to normal ones that they can self-regenerate and differentiate. Lately, cancer stem cells have been identified in the human prostate and ovarian cancers (53, 54). The development and testing of most traditional cancer treatments depends on their potential to shorten or/and erase most of the tumor population. However, these treatment approaches can easily miss cancer stem cells that seem to be most resistant and resilient to the available standard chemotherapeutic agents (55-57).

According to these data, blockage of the EGF pathway may lead to inhibition of tumor angiogenesis and metastasis (41). This notion has been confirmed in clinical studies when testing for the combination of gemcitabine with erlotibin, a distinct blocker of EGFR on the intracellular tyrosine kinase part of the receptor (58-60). The outcomes of a phase III randomized placebo control study by Moore and colleagues in 569 patients with PC showed that the aforementioned combination, compared with gemcitabine alone, improved survival: one-year overall survival was 23 *vs*. 17% (p=0.023) and median survival was 6.24 *vs*. 5.91 months (58). These were the first data showing a survival benefit over gemcitabine therapy. In 2005, erlotibin was the first targeted-therapy for PC with licensed approval from the FDA (41). Following these data, more studies were conducted, and are currently ongoing, aiming to further improve survival by testing more combinations and doses (17).

Insulin-like growth factor-1 receptor (IGF-1R). Insulin-like growth factor-1 receptor is a transmembrane tyrosine kinase receptor that has been found to be over-expressed in PC cell lines and human tissues (61, 62). In PC human tissues, the mRNA of the *IGF-1R* is 32-fold more abundant than in normal human pancreatic tissues (61). Stimulation of IGF-1R has been reported to increase cell development and prevent apoptosis. Hakam and colleagues showed that in the majority of human PCs (64%) the anti-apoptotic effect of IGF-1R expression, along with expression of c-Src (62), was mediated by activation of MAPK and phosphatidylinositol 3-kinase (PI3K), which is known to lead to survival. Another study highlighted the significant role of IGF-1R signaling in PC angiogenesis (12) while cell senescence is mediated through p38 phosporylation and p53 subsequent activation. Proliferation and expression of the vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) is induced by IGF-1R, which in turn is related to PC metastasis to the liver and very poor diagnosis (63). In mice, IGF-1R induced *de novo* pancreatic tumor implying that IGF-1R signalizing in human PC leads to more aggressive cancer cells with increased capability for metastasis (64). Targeting IGF-1R may be of therapeutic potential in the management of PC. In PC 2Rv1 cell lines, Beltran and colleagues showed that the inhibition of IGF-1R by the monoclonal antibody AMG 479 inhibited by approximately 80% the growth of PC. In addition, the amalgamation of AMG 479 with gemcitabine further inhibited tumor growth (65).

Vascular endothelial growth factor receptor (VEGF). VEGFR-1 (Flt-1), VEGFR-2 (KDR) and VEGFR-3 are the receptors of the VEGF family. An in-depth analysis has been conducted upon the VEGF family and its receptors showing the importance of these molecules in tumor angiogenesis. VEGF was expressed in approximately 90% of ductal pancreatic adenocarcinoma samples and was associated with liver metastasis and prognosis (66, 67). VEGF was found to be expressed both in tumor cells, as well as in endothelial cells (67). It was also detected in bone marrow-derived cells or mesenchymal stem cells. In pancreatic adenocarcinoma, the expression of VEGF-C and -D was found to be associated with lymph node metastasis, lymphatic invasion and venous invasion (68, 69).

Smith and colleagues conducted a meta-analysis on data obtained related to immunohistochemical tissue prognostic markers in PC. They included 11 studies of 767 patients with resected PC and showed that expression of VEGF was related to increased risk of 50% for poor survival (Hazard ratio HR=1.51; 95% Confidence interval CI=1.18-1.92). This

association was the strongest amongst the prognostic markers included in the analysis, *i.e.* bcl-2, bax, p16, p53, smad4 and EGFR. The authors concluded that VEGF expression has the most significant prognostic value in resected PC (70).

Given the aforementioned significance of VEGF in the progression of PC, the results from the first clinical trials on the therapeutic value of several VEGFR inhibitors are rather disappointing. The impact of bevacizumab, a humanized antibody against VEGF, was assessed first. Promising results were obtained from the mixture of bevacizumab and gemcidabine in a non-randomized trial with 52 patients as recorded by Kindler and colleagues. The 6-month survival was 77%, where 8.8 months was the median survival and 5.4 months was the median progression-free survival. Following these results, a double-blind, placebo-controlled, randomized phase III study was carried in 535 patients (71). No such statistically significant difference was found in this study; overall survival 5.8 in the combination *vs*. 5.9 gemcitabine alone, $p=0.95$ and progression-free survival 3.8 *vs*. 2.9 months, respectively, $p=0.07$ (72). The authors concluded that addition of bevacizumab into gemcidamine hardly offers a therapeutic advantage in advanced PC patients (Kindler *et al*.) (72). Neither did the triple combination of bevacizumab, gemcitabine anderlotinib prolong survival in the trial of Van Cutsem and colleagues (73). Overall, bevacizumab did not seem to provide sufficient benefit in PC management, while it has been associated with higher risk of treatment-related deaths (74, 75). Similarly, the VEGF inhibitors sorafenib and axitinib failed to demonstrate any therapeutic benefit in phase III trials, which indicates that targeting VEGF signaling might probably be an ineffective strategy for the management of PC (75-77).

A different investigational approach targeting VEGFR-2 with a new vaccine (VXM01) is currently ongoing by Niethammer and colleagues. Based on promising pre-clinical experiments, they assume that vaccination should enforce immune memory against proliferating cancer cells and disrupt existing vasculature. The vaccine combined with gemcitabine will be first given at a phase I double-blind, dose-escalated, placebo-controlled study in 45 patients with stage IV PC (78).

Other Receptors

Integrin α5β1. Integrins are heterodimeric receptors consisting of distinct chains called α (alpha) and β (beta) subunits. Each subunit contains two separate tails penetrating into the plasma membrane and possessing small cytoplasmic domains (79). In endothelial cells the integrins are chained by the ligands of these receptors and induce shape change, motility and growth. The characteristics like survival, migration and rates of proliferation in the endothelial cell are encouraged by the ligation of integrin α5β1 and, hence, influence angiogenesis mainly *via* the VEGF pathway (74). Cell survival is promoted through Bcl-2, migration through RhoA and proliferation through ERK, Akt and FAK-dependent mechanisms (80). Integrin α5β1 is found to be over-expressed in metastatic tumor cells in PC and its interaction with fibronectin encourages the senescence of growth-arrested cancer cells at the location of distant metastasis (81).

Somatostatin receptors. Somatostatin (SST) is important for carcinogenesis because it inhibits cell proliferation and angiogenesis (82-85). Five receptors (SSTR1-5) that mediate the action of SST have been identified in normal and malignant tissues (86). Molecular analogues of the SST molecule have been used as therapeutic agents against prostate cancer, breast cancer, neuroendocrine tumors and PC (82-86). Especially in PC treatment, inducing over-expression of serotonin receptors might be of therapeutic significance as it has been shown that mRNA levels of two of the five receptors (R2 and R5) are significantly lower in pancreatic malignant tissue in comparison with their levels in the surrounding healthy tissue (86).

SOM230, is a new somatostatin analogue that has the tendency to closely associate with SST1, SST2, SST3 and SST5 receptors. Presently this new somatostatin analogue is under evaluation going through phase I-III trials (87, 88). During this time, new and enhanced drugs are being developed that can interact with multi-receptor family cross-talk. In relation with internalization, agonist-induced desensitization and activity, these SST subtype homo- or heterodimers might have characteristics different from the individual receptors (89-91). A high-binding specialization is found in the SST2-454 and dopamine D2 receptors associated with BIM-23A387, which is a hybrid somatostatin–dopamine molecule. In comparison to SST2- and D2-specific analogues, it even has an enhanced potency on growth hormone and release of prolactin by the help of pituitary adenoma cells, be it alone or in combination. Although based on the binding affinity of the compounds for SST2 and dopamine D2 receptors, this enhanced particle cannot be described in details (92). Delivering chemotherapeutic compounds selectively upon tumor cells is the primary goal of targeted-chemotherapy, similar to the aim of peptide receptor-targeted radiotherapy (93, 94).

Death receptor 5 (DR5). DR5 is a trimetric transmembrane protein, which belongs to the tumor-necrosis-factor (TNF) receptor superfamily. It contains an extracellular domain that binds to its ligands and a cytosolic death domain that participates in an apoptotic signaling pathway. After being bonded by its ligand, TNF-related apoptosis-inducing ligand (TRAIL), the receptor forms a homotrimer, which induces the formation of a death-inducing signaling complex (DISC). The trimerization of the receptor death domain employs the

Fas-associated death domain (FADD) protein in the DISC that subsequently initiates caspase-8-triggered apoptosis (95).

The scientific interest in a potential anticancer activity of the DR agonists comes from: (i) their ability to particularly influence apoptosis of tumor cells and not other normal cells, (ii) their p53-free pathway of apoptosis and (iii) their potential to work along with chemotherapy agents and other targeted therapeutics, therefore improving their anticancer activity. After oncogene-mediated activation, MDM2 is inhibited by the p14ARF protein causing stability and, hence, initiating p53 (96). According to a recent study, ARF was important for suppressing tumor, whereas DNA damage-induced p53 response was dispensable (97).

DR agonist antibodies have been tested producing positive results in a variety of tumors including PC (98). In particular, in PC, the DR 5 agonists conatunumab (AMG 655), a monoclonal antibody, and CS-1008, a humanized monoclonal antibody, have been reached the phase II of clinical development, both in amalgamation with gemcitabine (69, 98). The phase II study of conatunumab plus gemcitabine produced positive results in terms of disease control rate (69%) and 6-month survival (76%). Following these first results, the investigators decided to compare the therapeutic potential of the combination of gemcitabine with either conatunumab or ganitunab, the inhibitor of IGF-1R, in a phase II randomized analysis. The 6-month survival was 59%, 57% and 50% in the conatunumab-, ganitumab- or gemcidamine-alone arms, respectively (77). A third single-chain antibody, apomab, is under pre-clinical evaluation (69).

Claudin receptor. Claudins (CLDNs) play a significant role in tight junctions, in cell apoptosis in different kinds of tumors, in invasion and metastasis of cancer. Tight junctions act as barriers between epithelial and endothelial cells but they also create pores and channels of various selectivity in-between cells. They have various characteristics like tissue-, organ- or cell-specific combination of proteins of the claudin, occludin, E-cadherin, tricellulin and JAM families. Signal transduction is conducted in a way that tight junctions are regulated and managed intracellularly and they in turn induce gene expression, proliferation and cell differentiation (99).

The expression pattern of claudins in tumor tissues, including pancreatic tumor cells, is distinct from that in normal tissues. Specifically, it seems that CLDN-1, -2 and -4 are specific markers of ductal differentiation; CLDN-1 of acinar and CLDN-3 of endocrine differentiation (100). Due to claudin's function as an adhesion molecule between different cells, it has been suggested that a reduction in its expression would facilitate cell detachment and promote tumor invasion (101). Indeed, lower CLDN4 expression is associated with shorter survival prognosis (HR=1.362; 95% CI=1.011-1.873; p=0.0419) (102). CLDN4 was over-expressed in PC and when its chimeric (mouse-human) monoclonal antibody KM3934 was introduced in xenografted mice, the tumor growth was inhibited (103-106).

Another interesting CLDN4-targeted therapy in PC is the *Clostridium perfringens* enterotoxin (CPE), a food poisoning for which CLDN4 is the specific receptor. CPE is toxic for PC cell lines expressing CLDN4 in a way depending on CPE dose and CLDN4 expression levels. CPE injection in PC xenografts leads to a reduction in tumor growth (101).

Notch receptors. The notch pathway is significant in the development of normal pancreatic tissue and also in PC initiation and invasion. Several ligands, expressed on neighboring cells activate the cell surface notch receptors in a signaling pathway that is essential to cell apoptosis, differentiation and proliferation. Upon notch receptors' activation, their intra-membrane domain is proteolytically cleaved allowing their active intracellular domain to move freely translocating into the nucleus. Once in the nucleus, it induces a variety of target genes. In pre-neoplastic lesions and in invasive PC, up-regulation of several of these selected genes takes place. The notch signaling pathway is involved in tumor vascularization and this function makes it a target for new drug development (39). Furthermore, there is evidence that notch signaling leads to the managing of the transformed phenotype of PC cells. This is supported by data showing that down-regulation of Notch1 receptors -with either specific siRNA or treatment with γ-secretase inhibitor- was correlated with lowered proliferative rates, higher apoptosis, reduced growth of anchorage-independent and reduced invasion features of PC cells (7).

Suppressor of Hairless in Drosophila includes the transcription of a variety of target genes, consisting those of hairy enhancer of split (HES) family of transcriptional repressors. In a precursor condition, these cells are sustained by the family members of HES. At the time of embryogenesis, the pathway is active but nothing takes place in the pancreas, however, up-regulation of many notch target genes will take place in pre-neoplastic lesions and in various invasive pancreatic cancers (107). Vascularization in tumors is even promoted by the notch signaling and is even regarded as a clear target for the purpose of developing new drugs (108).

Mesothelin receptors. Mesothelin is an anchored cell surface protein that is produced after the cleavage of a precursor protein encoded by the mesothelin gene (*MSLN*). The complete physiological roles of these proteins are yet not known. The levels of mesothelin protein and gene expression were elevated in ovarian, pancreatic, biliary and gastroesophageal cancer. While MSLN is not expressed in normal pancreas, it is expressed in pancreatic adenocarcinomas and bile duct adenocarcinomas as 100% and in ampullar adenocarcinoma as 89%. Furthermore, the

expression of MSLN in tumor tissues has a unique distribution pattern, making it thus a crucial target in diagnosis and treatment of the cancer (95).

FSH receptor. Radu and colleagues have recently reported the expression of the follicle stimulating hormone (FSH) receptor in the peri-tumor blood vessels, from a large group of human tumors (109). They examined 1,336 patients suffering from different types of cancer and showed that the FSH receptor was expressed even in the early phase T1 tumors of the prostate, breast, colon, pancreas, urinary bladder, kidney, lung, liver, stomach, testis and ovary. In addition, its expression was not extended to the healthy tissues surrounding the tumors in a distance of ≥10 mm. The exact role of FSH in tumor progression is not yet clear. However, given their selective expression in normal tissues near the tumor, it has been suggested that the FSH receptor can be used in tumor imaging. Administration of antibodies against FSHR can make PC visible at its early stages. In addition, FSH expression could effectively guide the intravenous delivery of therapeutic agents against PC (110).

MUC1 receptor. MUC1 is a type I cell surface membrane glycosylated protein expressed in glandular epithelial tissues and throughout the gastrointestinal tract (95). MUC1 is over-expressed over the entire surface of human adenocarcinomas in which it promotes tumor cell survival and proliferation (111-113). According to an updated report, after being stimulated by TNF-a, MUC1 binds to the TNF-R1 complex and further combines with the IκB kinase for degrading IκBα that supports cell survival. Moreover, death receptor-mediated apoptosis is blocked by the bonding between the MUC1 and caspace-8 and FADD. In PC, MUC1 interacts with myelin-associated glycoprotein promoting, thus, perineural invasion (95). Therefore, targeting MUC1R expression in PC may inhibit tumor growth.

ADM receptor. Adrenomedullin (ADM) is over-expressed in PC and has a strong autocrine role in this disease. ADM is a peptide ligand for cell surface receptors mediating growth and metastasis of the tumor. These receptors are the adrenomedullin receptor (ADMR, also known as L1-R) and the calcitonin- receptor-like receptor (CRLR). Interestingly, it has been shown that PC cells express only ADMR (114). Therefore, ADMR may be a useful target treatment of PC since its inhibition could control tumor growth and metastasis (115).

Farnesoid X receptor. A nuclear receptor known as farnesoid X receptor (FXR) belongs to the superfamily of ligand-dependent transcription factors. It is highly expressed in the liver, gut, kidney and adrenal cortex, where its function is to regulate genes acting in bile acid homeostasis, lipid and glucose metabolism. An impact on tumor growth was recently reported, mainly on colorectal tumor cells and PC cells. Thus, the path leading from bileacid-induced stimulation of the FXR towards first the carcinogenesis and later on the metastasis is still unclear. The consequences of FXR silencing and inhibition on PC proliferation, migration and invasion are currently being examined (116).

Transferrin receptor. The membrane transferrin receptor (TFRC) is over-expressed in proliferating cells. Therefore, the detection of its expression may offer a valuable tool in the diagnosis and possible therapy of solid tumors. TFRC is also highly expressed in pancreatic tumor cells, which showed positive (82%) or heterogeneous (11%) expression of this receptor. Primary and metastatic tumors display over-expression of TFRC, whereas normal stromal and endothelial cells do not show any such over-expression. High expression of TFRC is often found in PC and neuroendocrine carcinoma but not in normal pancreatic tissues and benign neuroendocrine tumors of the pancreas. This specificity in expression makes TFRC a potential marker of malignant transformation and, therefore, it could potentially be used for the diagnosis and therapy of PC (117).

Sigma-2 receptors. The sigma-2 receptors are highly expressed in rapidly proliferating cells and down-regulated when cells become quiescent. These receptors have been found to be expressed in various human cancer cells such as breast, brain, bladder, colon and melanoma. They are also highly expressed in both human and murine pancreas cancer cell lines. S ligands of the sigma-2 receptors have been found to mediate apoptosis and, therefore, could probably be used as sensitizers to standard chemotherapies. Therefore, sigma-2 receptors can be considered potential targets for the treatment of PC (118).

Chemokine receptor CXCR4. Chemokine CXCL12 and its receptor CXCR4, mediate invasiveness and metastatic behavior in PC cells. It has been shown that in pancreatic intraepithelial neoplasias (PanIN) both the CXCL12 and CXCR4 are expressed at the time of PanIN progression when their frequency increases. CXCL12/CXCR4 expression has been recorded from the pre-invasive stages of PC. More studies are needed to better-underline the function of CXCR4 signaling in the progression of PanIN and clarify whether CXCR4 can possibly be used as a target for chemoprevention and early-stage therapy in PC (119).

Urokinase plasminogen activator receptor. A cellular receptor known as urokinase plasminogen activator receptor (uPAR) is expressed in PC, as well as tumor stromal cells. uPAR activation is required for PC cell migration and invasion. Studies have investigated whether uPAR inhibition leads to

limited growth of PC (120, 121). Experiments in mice showed that anti-uPAR therapy markedly decreased orthotopic growth of human PC, while completely inhibited retroperitoneal invasion and decreased liver metastases. The decrease in tumor growth is mediated by a direct inhibition of tumor cell proliferation. Therefore, there is a need for continuing the study on the uPAR activity in human PC (121).

Ephrine A2 receptor. The Eph A2 receptor, member of the ephrine tyrosine kinases receptor family, interacts with cell-bound ligands known as ephrins (122). EphA2 is a receptor involved in the process of embryogenesis and is up-regulated in PC and many solid tumors, including esophageal squamous cell carcinoma and prostate, breast, prostate, colon, lung, skin, cervical andovarian cancers (122-124). The EphA2 receptor is believed to be involved in the development of tumor and metastasis (124).

GRIA3 receptor. GRIA3 is a subunit of ionotropic glutamate receptor, also called α-amino-3- hydroxy-5-methyl-4-isoxazol-propionate (AMPA) receptor (AMPAR), and is one of the four AMPAR subunits, which combine to form heterotetramers (125). GRIA3 is involved in PC cell survival, proliferation and migration. GRIA3 is also a downstream target of CUX1, known to play a crucial role in a comprehensive and difficult transcriptional program that improves the progression of tumor (126). CUX1or CUTL1 hails from an evolutionarily conserved family of transcription factors participating in the regulation of cell proliferation, embryonic growth and cell differentiation (127). Targeting GRIA3 may even present an interesting novel therapeutic approach for PC depending on higher expression and the strong impact of GRIA3 on proliferation, survival and migration (126).

RON receptor. The RON receptor is a tyrosine kinase and is over-expressed in most PCs. This is the reason why the RON pathway has recently gain attention as a potential novel therapeutic target in PC. RON has a vital function in the K-Ras pathway and the RON ligand induces migration, invasion and apoptotic resistance in the pancreatic cells. The pathobiological importance of RON over-expression in PCs has not been fully understood. Although RON over-expression in PC has been shown, because of conflicting studies, it is not known yet whether the RON ligand increases proliferation in PC cells. However, there is preliminary evidence that RON-directed therapies could probably play a role in the reduction of human PC xenografts' growth (128).

Angiotensin II receptor AT-1. Angiotensin II (Ang-II) mediates the function of the system of renin-angiotensin and is essential to the pathophysiology of cardiovascular and renal systems. AT1 and AT2 are the main subtypes of Ang-II receptors. It has been recently shown that the role of Ang-II and its receptors is not restricted to cardiovascular field but is extended in cancer (129). It is known that AT-1 is expressed in human PC and also regulates PC growth (129-132). Fujimoto and colleagues showed, for the first time, that "AT1R regulates the growth of PC". Their experiments were performed in PC cell lines and in human PC tissues; results were compared against normal controls. They further showed that the blockage of the AT1R with a selective antagonist suppressed tumor growth (129). Arafat and colleagues showed that AT1R was over-expressed in 75% of patients with pancreatic ductal adenocarcinoma. Because the immunohistochemical staining of the AT1R was co-localized with ACE and VEGF staining, the authors suggested a putative role of the angiotensin II-AT1R-VEGF system in PC angiogenesis. Also, they found that blocking of the AT1R reduced PC cell viability (133).

Further studies have shown the involvement of the RAS system in tumor angiogenesis. Research is ongoing in this field, while modern translational research is expected to shed light on the role of this system in cancer (134). It was shown that the risk of cancer was reduced in patients treated with ACE inhibitors (135). Moreover, the addition of RAS blockers, either with ACE inhibitors (ACEIs) or AT1R blockers (ARBs), in PC therapy with gemcitamine prolonged survival in patients with advanced PC and hypertension (15 months in patients receiving ACEI/ARB compared with 8.9 months in patients without ACEI/ARB) (136).

NR4A orphan receptors. The family of NR4A nuclear receptors consists of the NR4A1 (Nurr77, NGFI-B, TR3), NR4A2 (Nurr1, NOT) and NR4A3 (Nor-1, MINOR) receptors. In many tumor types, NR4A receptors are involved in the regulation of apoptosis (137). NR4A1 controls survival and death of cancer cells and is over-expressed in PC (138). The tumor suppressor function of NR4A1 and NR4A3 is indicated by the fast development of myeloid leukemia in double-knockout mice. Targeting NR4A1 may inhibit growth of pancreatic and other cancers (139, 140). Recently identified pro-apoptotic agents, such as DIM-C-pPhOH that induce NR4A expression, have been proposed as potential novel chemotherapeutic therapy in pancreatic and other cancers (141-143). Especially the TR3 receptor is considered to be a unique target for treatment in PC. Current studies investigate drugs targeting TR3 for the treatment of PC (138).

Peroxisome proliferator-activated receptors (PPARs). PPARs, which are ligand-activated nuclear receptors, belong to the steroid receptor superfamily (144). PPARα, PPARβ and PPARγ are the three PPAR isotypes that have been identified (145). Distinct pattern of expression and distinct ligands have

been noticed in the three isotypes (144). PPARγ is greatly expressed in the adipose tissue and has a significant function in the distinction of adipocytes, monocytes, macrophages and in insulin sensitization (144-146). PPARγ is expressed in most malignancies and highly expressed in PC. Kristiansen and colleagues reported 71.3% expression of PPARγ in 129 immunohistochemically stained human PC tissues. Higher expression of PPARγ, related with shorter survival, was found in the survival analysis conducted by these investigators and they suggested that PPARγ could serve as a marker for patients' prognosis (147). Similarly, Giaginis and colleagues showed that PPARγ was expressed as high as 75% in 65 human PC tissues. The expression of PPARγ was higher in more severe tumor grades. In addition, higher expression was associated with shorter survival, while PPARγ was an independent prognostic factor for survival (148). PPARγ action is mediated though its heterodimer with the retinoid acid receptor (RXR) (145). Ligands to this heterodimer could possibly be used in PC treatment (147). Indeed, the activation of the PPARγ pathway is shown to inhibit the growth of PC in several studies designed to assess the effect of PPARγ ligands on pancreatic tumor pathogenesis in both *in vitro* and *in vivo* studies (145, 149, 150). The VEGF pathway is one possible pathway through which suppression of tumor angiogenesis is mediated (145).

Estrogen receptor (ER). ER belongs to the family of nuclear ligand-inducible transcriptional receptors (151). Greenway and colleagues were the first scientists to describe high presence of estrogen receptors in pancreatic malignant tissue in humans (152). Subsequent reports were conflicting probably due to the experimental methods used. In pancreatic ductal adenocarcinoma, the first reports were on studies where the presence of ER was indicated indirectly *via* the binding assay technique. Later, with the development of specific ER antibodies, the presence of ER was assessed through immunohistochemistry using antibodies for only the ER-α isoform; most of these studies did not find any ER-α staining. In contrast, in other studies, ER mRNA was detected. In particular, *ER-β* mRNA levels were higher than those found in ER+ and ER– breast cancer tissues; these levels, however, were decreasing as the tumor progressed in more advanced stages (153). In papillary cystic neoplasms, intra-ductal papillary mucinous tumors and mucinous cystic tumors of the pancreas, most studies did not detect ER. However, again the antibodies were ER-β specific. In contrast, Morales and colleagues used both antibodies against α- and β- isoforms (154).

The results from clinical and experimental studies on the effects of anti-estrogens tamoxifen and phytoestrogens further supported that estrogens have an important function in PC (153). Although no advantage of survival was retrieved by the randomized-controlled trials with tamoxifen, non-randomized studies demonstrated the opposite (155-160). These results are difficult to interpret given the controversy of data with regards to ER-α and -β expression in pancreatic adenocarcinoma (153). Konduri and colleagues suggested that the ratio of ER-β/ER-α may predict a response to estrogen-related therapy in the treatment of PC (161). Therefore, there is a need for better understanding of the ER expression in PC that would enhance our knowledge in clinical implications of anti-estrogen drugs in this cancerous condition.

Discussion

It is very important to identify the specific target molecules present on the tumor cell surface, and not inside the normal tissue stroma, that is associated to oncogenesis of PC, tumor growth or resistance to chemotherapy. It is also imperative to discover the molecules participating in controlling inflammation and host immune responses. Since most of these receptors enhance proliferation and tumor progression, numerous studies on the blockade of these receptors by specific inhibitors are currently being conducted (130, 162, 163). Although in the PC treatment, especially in pre-clinical research studies related to selected molecular with monoclonal antibodies progress has been made, yet more work is required for the delineation of their role in the enhancement of PC patients' survival.

With the identification of the molecular receptors associated with PC, more target molecules that play critical roles in tumor pathophysiology and senescence-associated signal transduction in cancer cells will be detected. This might enable the development of molecular-targeting techniques utilizing monoclonal antibodies, which will be extremely useful for the diagnosis and treatment of cancer. Indeed, for PC, a combination regimen using monoclonal antibodies against specific receptors and radiotherapy or conventional chemotherapy has been determined. Further efforts to investigate target molecule expression, mutations and dynamic changes in the development of the cancer might permit researchers to recognize reliable biomarkers that can give guidance for combination treatment with monoclonal antibodies and other cytotoxic agents (39, 95). Such practices are known to reduce the systemic side-effects of conventional chemotherapy and enhance efficiency.

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Received August 14, 2014
Revised September 22, 2014
Accepted September 26, 2014