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Invited critical review

The role of protein kinases in pancreatic carcinogenesis

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Abstract

Background: Pancreatic cancer is a devastating disease with a very poor prognosis.
Methods: Protein kinases are aberrantly expressed in pancreatic ductal adenocarcinoma as analyzed by microarray-based expression analysis and have an impact for pancreatic cancer. Many regulatory proteins have an impact on cancer progression similar to the kinases. The list contains several regulators of kinases derived from the cell cycle control or the mitogen-activated protein (MAP)-kinase pathway.
Conclusion: Both signalling pathways are essential for tumor progression and pancreatic ductal adenocarcinoma (PDAC) malignancy.

Keywords: Pancreatic ductal adenocarcinoma; Protein kinases; Cancer progression; Signalling pathways; Microarray analysis; Survival

Contents

1. Pancreatic cancer

Patients suffering from pancreatic cancer face a very poor prognosis. Pancreatic ductal adenocarcinoma (PDAC), making up to 70% of all cases of pancreatic cancers is not only the most common form of pancreatic cancer but also the one with the worst prognosis. With a 5-year relative survival rate of <5% and a 20-year survival of <3% it is one of the worst cancer entities [1]. After reinvestigating the tumor samples from "survivors of PDAC" from a collective of patients from Finland, specialized pathologists concluded that the surviving patients mostly did not suffer from PDAC but other, less malignant forms of pancreatic cancer, thus pointing the survival rate of PDAC closely to zero [2]. With >33,700 estimated new cases in 2006 and estimated 32,300 deaths in 2006, pancreatic cancer ranks 10th in the statistics of new cases and 4th in the statistics of cancer related deaths in the US [3]. While smoking and alcoholism could be identified as a risk for pancreatic cancer [4], only minor changes in the annual age-adjusted cancer death rate could be found during the last century in contrast to other lifestyle cancers like lung cancer.

Apart from surgery there is no effective therapy for pancreatic cancer, but even patients who underwent surgery often die within 1 year postoperatively. Because the malignancy is usually in an advanced state when diagnosed, the surgical respectability is <20%. But because of the occurrence of local recurrences and/or distant metastases after surgery, also R0 resected patients face a poor life expectancy [5,6]. Furthermore, this cancer entity is also characterized by a high resistance to all common chemotherapeutical drugs [7–10].

To get further insights into the molecular aberrations responsible for the induction and progression of pancreatic cancer and to

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identify targets for an effective future therapy, we and others analyzed the expression pattern of normal and cancer tissue by microarray analysis [11–15]. Another study focussed on aberrant expression patterns found in PaNIN-lesions, the non-malignant precursors of pancreatic ductal adenocarcinomas [16]. In this review, we focus on protein kinases, their function and regulation in cell homeostasis and the putative meaning of their deregulation in pancreatic cancer. The function of proteinases found to be deregulated by several single expression studies [11,12,14,15,85,86] and a meta-analysis [13] will be discussed.

2. Protein kinases

Protein kinases are a heterogeneous group of enzymes that can add phosphate groups to the hydroxyl group of amino acid residues in proteins. It was estimated that up to 2% of the genes encode for protein kinases [17,18] and that roughly 30% of the cellular proteins could be modified by kinases. According to different criteria as their involvement in the homeostasis of the cell or their substrates the protein kinases are grouped into different families: serine/threonine-specific kinases, tyrosine-specific kinases, aspartic acid-/glutamic acid-specific protein kinases, histidine-specific protein kinases and so-called mixed kinases are known. The specificity of the last is not restricted to one specific amino acid residue but they can phosphorylate several.

Serine/threonine-specific kinases are defined as enzymes that phosphorylate serine or threonine residues in proteins. The phosphate donors are nucleotides, mostly ATP (http://www.nlm.nih.gov/mesh/2006/MBrowser.html). Serine/threonine-specific kinases are involved in many signal transduction pathways related to growth control and cell cycle progression. This family consists of the MAP kinases, which are involved in growth factor signalling, the cyclin-depending kinases, which are involved in the regulation of cell cycle progression or enzymes that regulate DNA repair or induction of apoptosis. Indeed, members of the MAP kinase family (e.g. MAP4K4 and MAPK9) and the CDKs (e.g. CDK7) are aberrantly expressed in PDAC (Table 1). The current Medical Subject Headings (MeSH 2006) nomenclature includes the following 22 serine-/threonine-specific kinases: activin receptors, bone morphogenetic protein receptors, Ca(2+)-calmodulin-dependent protein kinase, casein kinases, cyclic nucleotide-regulated protein kinases, cyclin-dependent kinases, DNA-activated protein kinase, eIF-2 kinase, glycogen synthase kinases, I-kappa B kinase, MAP kinase kinase kinases, mitogen-activated protein kinase kinases, mitogen-activated protein kinases, oncogene protein v-akt, phytochrome A, proline-directed protein kinases, protein kinase C, proto-oncogene proteins c-akt, proto-oncogene proteins c-bcr, proto-oncogene proteins c-pim-1, rhodopsin kinase and the ribosomal protein S6 kinases.

Protein kinase D1 (PRKD1), a member of the protein kinase C family has been shown to be significantly upregulated in PDAC cell lines highly resistant to chemotherapeutic drugs (Panc89, PancTuI), while PDAC cell lines which proved to be less resistant (Colo357, Capan-1) also express lower levels of this kinase. Overexpression of PRKD1 in Colo357 cells shortened the doubling time and increases the expression of anti apoptotic proteins like cFLIP and SURVIVIN [10], underlining the impact of this serine/threonine-specific kinase for pancreatic cancer. Another member of this family, also upregulated in PDAC (Table 1) is the casein kinase 1 (CSNK1). This kinase has been found to be responsible for centrosome- and mitotic spindle abnormalities [19,20]. Casein kinases interact and influence the activity of numerous tumor relevant genes, namely TP53 [21], BRCA1 [22] or FGF-1 [23].

Tyrosine-specific kinases catalyze the phosphorylation of tyrosine residues in proteins. The donor is either ATP or another nucleotide. According to the MeSH nomenclature this family consists of 7 members: focal adhesion protein–tyrosine kinases, mitogen-activated protein kinase kinases, proto-oncogene proteins c-fes, receptor protein–tyrosine kinases, proto-oncogene proteins c-abl, src-family kinases and the ZAP-70 protein–tyrosine kinase.

This family consists of many important regulators which are involved in numerous tumor relevant signalling pathways. Indeed, many cellular growth factor receptors are tyrosine kinases. Upon ligand binding these receptors dimerize, leading to activation of the kinases, transphosphorylation of the monomers and in the following to the activation of the downstream pathway. The different pathways vary in the proteins and individual mechanisms involved but in general, the modified receptor is recognized by specific proteins which act as a linker to other components of a pathway. As an example, binding of EGF to its receptor induces receptor dimerization and phosphorylation which could be recognized by Grb2 and Sos1 leading to activation of the Ras/Raf pathway and in the following several intracellular serine/threonin-specific protein kinases like MAP kinase kinases. In the end, modifications of transcription factors like Elk 1 or SAP 1/2 induce transcriptional changes in the nucleus. EGFR does indeed play an important role in metastasis and recurrence of PDAC [24]. Other prominent members of this family are the insulin receptor (IGF1R), the PDGF-receptor or the VEGF-receptor.

Several mechanisms leading to an aberrant activity of tyrosine receptor kinases have been described. Thus, mutations of the receptors can cause ligand-independent dimerization (one exception is the IGF-receptor, which exists as dimer even in the absence of its ligand) and constitutive activation of the receptor. Such mechanism has been described for several tyrosine kinase receptors, e.g. RET [25]. Gene translocations leading to a fusion of parts of a tyrosine kinase receptor with a partner that can cause dimerization can also be responsible for a ligand independent activation. Such translocations with one partner being a tyrosine kinase receptor include e.g. fusions of PDGF-Rα (platelet-derived growth factor receptor alpha) with BCR (breakpoint cluster region; a serine-/threonine-kinase with yet unknown function), FGF-R3 (fibroblast growth factor receptor 3) with ETV6 (ets variant gene 6) [26], FGF-R1 (fibroblast growth factor receptor 1) with BCR, Ret (ret proto-oncogene) with KTN1 (kinectin) [27] or JAK2 with PCM1 (pericentriolar material 1) [28].

Another important way of growth activation are autocrine stimulatory mechanisms. Many tumors produce and release high amounts of growth factors, leading to the activation of the tyrosine