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Mini-review

Epidemiological-molecular evidence of metabolic reprogramming on proliferation, autophagy and cell signaling in pancreas cancer

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ABSTRACT

Pancreatic cancer remains one of the deadliest human cancers with little progress made in survival over the past decades, and 5-year survival usually below 5%. Despite this dismal scenario, progresses have been made in understanding of the underlying tumor biology through among other definition of precursor lesions, delineation of molecular pathways, and advances in genome-wide technology. Further, exploring the relationship between epidemiological risk factors involving metabolic features to that of an altered cancer metabolism may provide the foundation for new therapies. Here we explore how nutrients and caloric intake may influence the KRAS-driven ductal carcinogenesis through mediators of metabolic stress, including autophagy in presence of TP53, advanced glycation end products (AGE) and the receptors (RAGE) and ligands (HMGB1), as well as glutamine pathways, among others. Effective understanding the cancer metabolism mechanisms in pancreatic cancer may propose new ways of prevention and treatment.

Introduction

Pancreatic cancer is the second most frequent gastrointestinal cancer in the western world and one of the deadliest of human solid cancers. For practical reasons (and for the sake of this mini-review) we will consider pancreatic ductal adenocarcinoma (PDAC) when talking about pancreatic cancer as almost 95% of invasive cancers stem from this histological type. What makes pancreatic cancer stand out compared to other solid malignancies is the remarked lack of clinical progression over the past decades in terms of improved survival. Indeed, the lethality of pancreatic cancer remains very high [1,2]. True 5-year survivors are exceptionally few (usually well below 5%), even for those undergoing curative surgery [2,3]. The reasons for this dismal prognosis are manifold and include a largely inaccessible organ positioned retroperitoneally with little or no direct access for investigation and early detection; presentation of symptoms that often occur at a late stage when metastatic disease is already present, or, when curative surgery is not feasible due to infiltration of neighboring organs or vascular structures; and, lastly, few available chemo-radiation regimens with good clinical response to control metastatic disease. In addition comes the long-standing ignorance of the biology behind pancreatic carcinogenesis.

However, developments and innovations over the past few years are changing the future prospects of pancreatic cancer outcomes. Among these are the increased understanding of the precursor lesions (called pancreatic intraepithelial neoplasias; PanINs) in the step-wise progression model (see Fig. 1) from pre-neoplastic to invasive disease [4,5]; the increased understanding of molecular signaling pathways and their associated genetic complexity [6–8], and; novel ways to administer chemotherapeutic substances to patients [9] and development of novel animal models for future improved effects [10]. Furthermore, an increased understanding of the underlying biology [11] now includes the genomic complexity of the disease, the role of pancreatic cancer stem cells, the relevance of the tumor microenvironment and, last but not least, the unique metabolic adaptation of pancreas cancer cells to obtain nutrients under hypoxic environment [12–14]. Research into cancer metabolism has gained increased interest in general as cancer cells are known to alter their metabolism as a generic hallmark for prolonged survival, thus a better understanding of this may pose new ways of targeting cancer as a disease [15,16]. Targets for such intervention may come from increased

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knowledge in any of the described "Cancer Hallmarks" [17]. These hallmarks now include 'reprogramming of energy metabolism' and 'evading immune destruction' in addition to the 'tumor microenvironment'.

Herein, we will give a brief overview of the current role of cancer metabolism in relation to pancreatic cancer development, metabolic risk factors, putative metabolic pathways and their players and, lastly, the potential role for prevention or treatment.

Epidemiological risk factors for pancreatic cancer

Epidemiological research has revealed a number of risk factors for developing pancreatic cancer [18], of which some are established and others suspected or merely associated without direct confirmed causation (see Table 1). Importantly, some of these strong risk factors are modifiable, such as smoking (reduced risk with quit smoking), obesity (reduced risk with leaner body figure, lower BMI and increased physical activity) and diabetes mellitus (reduced risk by increased glycemic control through anti-diabetic measures). Some of the risk factors (Table 1) will be briefly discussed further in relation to the potential influence on cancer metabolism, including the role of obesity, diabetes, and dietary factors. Also, available evidence from the EPIC (European Prospective Investigation into Cancer and Nutrition cohort) and the PanScan (National Cancer Institute Pancreatic Cancer Cohort Consortium) consortia will be presented.

Dietary intake and risk in pancreatic cancer

In the PanScan consortia, the largest nested case-control study available, the association between BMI, anthropometric factors, and pancreatic cancer risk was analysed. A strong correlation between BMI and a risk of pancreatic cancer was observed when comparing individuals with lowest vs. highest BMI quartile for both sexes (OR 1.33 vs. 1.34 for men vs. women). In addition for women a risk with increasing hip to waist ration was observed (OR 1.87) [19]. Although these results indicate the central role of an excess energy intake in the risk of pancreatic cancer, data concerning effects of diet on the risk of pancreatic cancer are fairly inconsistent between various cohorts. Dietary habits, including high consumption of red meat, have been proposed as risk factors for pancreatic cancer. However, in an EPIC study, findings did not support the conclusion of the World Cancer Research Fund that red or processed meat consumption increase the risk of pancreatic cancer [20].

Table 1
Risk factors for pancreatic cancer.

Established factors
Age
Hereditary syndromes
Cigarette smoking
Obesity
Diabetes mellitus
Suspected factors
Alcohol
Pancreatitis
Dietary factors
Meat
Fruits
Flavonoids, Folate, Lycopene
Carbohydrates
Glycemic index/load
Other factors
Infectious agents
Occupation
Allergy
Drugs/medications
NSAIDs
Statins
Metformin

There are discrepant results concerning the risk of alcohol on developing pancreatic cancer with smaller series showing an increased risk. However, in PanScan no significant overall association between total alcohol intake and pancreatic cancer risk was found, although a statistically significant increase in risk was observed among men with high consumption of liquor. No associations were noted for wine or beer intake [21]. This is in line with data from others pointing to no increased risk is observed in moderate consummation [18]. Excessive intake of alcohol is also associated with chronic pancreatitis, which again is associated as risk factor for pancreas cancer, possibly through the increased inflammatory milieu and fibrosis generated in the pancreas.

Acrylamid has been labeled a potential human carcinogen and has been discovered at relatively high concentrations in some starchy, plant-based foods cooked at high temperatures. However, in the EPIC study it was not confirmed as risk factor for pancreatic cancer [22]. Previous suspected risks with coffee and tea consumption were also not confirmed in the EPIC cohort [23].

Folate and related nutrients (homocysteine, cysteine, methionine, cobalamin, and vitamin B6) are believed to influence carcinogenesis through one-carbon metabolism (OCM), based on the function of OCM in DNA repair, methylation and nucleotide synthesis. Although the results are inconsistent, previous studies show inverse associations with pancreatic cancer and dietary folate. However, in the EPIC study an U-shaped association between plasma folate and pancreatic cancer risk in both men and women was observed [24]. Genes and single-nucleotide polymorphisms (SNPs) related to OCM have also been characterized in relation to pancreatic cancer with mixed results. In a recent PanScan based study, an association between OCM related SNPs and pancreatic cancer was observed in the analysed cohort-nested studies, but could subsequently not be replicated in case-control studies [25]. Therefore no strong evidence was found in this large study that genes related to OCM play a role in pancreatic carcinogenesis.

Diabetes and metabolic interaction with obesity and inflammation in pancreatic cancer

There is a well-known correlation between diabetes and pancreatic cancer. It should be noted that diabetes can act both as an early manifestation of pancreatic cancer, and as a modest risk factor for pancreatic cancer. However, relatively independently of obesity and insulin resistance, which are the classic and major risk factors for type 2 diabetes, moderate increases in pre-diagnostic HbA1c levels are associated with increased risk for pancreas cancer [26]. Similar findings were derived from 5 different cohorts [27], thus suggesting that circulating markers of peripheral tissue insulin-resistance are associated with risk for later pancreatic cancer. In a recent PanScan study, the association between pancreatic cancer and diabetes was studied prospectively. Self-reported diabetes was associated with an OR 1.40 of developing pancreatic cancer. The strongest association (OR 1.79) was observed for recently (2–8 years) diagnosed diabetes [28]. These results even further support a relationship between newly diagnosed diabetes and pancreatic cancer risk.

The rapidly developing use of genome-wide association (GWAS) studies allows for analysis of genetic pathways associated with disease. In a GWAS analysis from the Pancreatic Cancer Case Control Consortium (PanC4), genetic pathways related to pancreatic cancer were studied in 2028 cases and 2109 controls by using

likelihood-ratio test nested in logistic regression models and Ingenuity Pathway Analysis (IPA). The major finding was an interaction of the inflammatory response pathways with obesity, and insulin resistance or cancer-related pathways with diabetes in regards of risk of pancreatic cancer [29].

In GWAS data based on the PanScan consortia, the importance of the pancreatic development pathway, consisting of genes (such as *NR5A2*, *HNF1A*, *HNF4G*, *PDX1* and *HNF1B*) related to pancreatic development and differentiation, was shown for pancreatic cancer risk. Most interestingly, some of these genes also are closely related to the development of certain types of maturity onset diabetes of the young (MODY), type II diabetes, BMI and glucose metabolism [30]. Taken together these GWAS results indicate that the previous epidemiological correlations observed between diabetes, obesity and pancreatic cancer could partly be explained by activities in genetic pathways.

At the crossroads between obesity, inflammation and diabetes stands the cytokine called adiponectin, a molecule that has raised interest as a marker for pancreatic cancer risk. Adiponectin is exclusively secreted by adipocytes with anti-diabetic and anti-inflammatory properties. In the EPIC study the relationship of pre-diagnostic adiponectin levels with pancreatic cancer risk were studied, and an inverse association of elevated adiponectin levels with pancreatic cancer risk among never smokers was found [31]. The converging roles of inflammation, obesity, diabetes on the risk of pancreatic cancer was also shown in an EPIC study of prediagnostic blood levels of C-reactive protein (CRP), interleukin-6 (IL-6), and the soluble receptors of tumor necrosis factor-a (sTNF-R1, R2). Whereas CRP and IL-6 do not seem to play a role, with respect to risk of pancreatic cancer, sTNF-R1 seemed to be a risk factor in women and sTNF-R2 a mediator in the risk relationship between overweight and diabetes with pancreatic cancer [32].

Advanced glycation end products (AGE) and the receptor (RAGE)

Other substances of importance for both glucose metabolism and inflammation are advanced glycation end products (AGE) and their receptors RAGE. AGEs are formed by nonenzymatic reactions of reduced sugars and can be formed both exogenously (dietary AGEs from thermally processed food and tobacco) and endogenously by many cells in most tissues. There is an increased endogenous AGE formation during hyperglycemia. RAGE is an important inflammatory mediator that modulates crosstalk between prosurvival pathways, such as the IL6-pSTAT3 and autophagy, in pancreatic cancer tumor cells and contributes to early PanIN formation [33]. In the absence of RAGE, tumor formation is considerably delayed [34].

In recent years the involvement of the AGE-RAGE pathway in cancer has gained interest, as the AGEs are believed to exert their pro-inflammatory effects through activation of the RAGE. In an EPIC study, the pre-diagnostic blood levels of the AGE product CML (Ne-(carboxymethyl)lysine) and the secreted receptor for AGE (esRAGE), which functions as decoy RAGE receptor in vivo, were measured. A tendency of increased levels of CML and a reduction in pancreatic cancer risk (OR 0.57) was observed, but no association for esRAGE (OR 0.98) [35].

Pancreatic carcinogenesis through altered metabolism

Several subtypes of exocrine and endocrine pancreatic cancers are now recognized, as knowledge has developed. Only recently has the precursor lesions to PDAC been defined and histomorphologically described [36], known as Pancreatic Inraepithelial Neoplasia (PanINs; Fig. 1) and associated with distinct molecular alterations [5,37]. Indeed, this development in definition has spurred a large number of research into the progression steps in pancreatic cancer [4,38–43]. Further knowledge has been strengthened by full-genome and exome sequencing studies [6,44] and time-progression estimates from pre-neoplasia to invasive disease [45]. More recently, attempts at subtyping pancreatic cancer has been suggested [46], yet many of these studies need clinical validation or to be reconfirmed in other cohorts. However, the described discoveries may be used as stepping-stones for furthering the understanding of pancreas cancer biology and how this may be interfered to halt progression and increase survival.

Metabolism in pancreatic cancer – clues from metabolomics

By the time of diagnosis pancreatic cancer patients demonstrate many metabolic alterations including signs of muscle wasting, cachexia, changes in lipid metabolism, glucose metabolism and fatigue. These changes cause alterations in levels and distributions of metabolites, which can be measured with the metabolomic techniques. Increased levels of several metabolites have been found, such as arachidonic acid, which is central for compounds involved in inflammation and, also, increased levels of glutamine as reflections of the states of hypoxia, glycolysis and glutaminolysis in PDAC [47]. Glutamine levels were also found significantly altered with higher sensitivity and specificity than CA 19-9, the only currently clinically used tumor marker. The diagnostic accuracy increased further by combining multiple markers in a model, thus differentiating not only between patients with pancreatic cancer and controls, but also between those with pancreatitis [48].

Notably, as technological advances has given the opportunity for novel and advanced analyses of multiple components in any sample, metabolomics profiles have been sought in serum, tissue and urine for cancer-specific panels that could have influence on diagnosis, prognosis and therapy. Such studies have been performed in serum [49,50], tissue [51] and urine [52,53]. In a study using gas chromatography mass spectrometry (GC/MS) on serum samples from patients with pancreatic cancer Kobayashi et al. [49] investigated a diagnostic model based on four serum metabolites (xylitol, 1;5-anhydro-D-glucitol, histidine and inositol) and found the profile to outperform both CA 19-9 and CEA for diagnosis.

A further comprehensive study explored metabolites and transcriptomic profiles of tumor and non-tumor tissue in patients undergoing resection in two independent cohorts [51]. The investigators found specific alterations in the metabolites to free fatty acid (FFA) metabolism, which was decreased in cancer patients [51]. Altered lipid metabolism network included key lipolytic enzymes (such as PNLIP, CLPS, PNLIPRP1, and PNLIPRP2). Gene expressions of these lipases were significantly decreased in pancreatic tumors as compared with non-tumor tissues, leading to a reduction in FFA. A lower gene expression of PNLIP in tumors was additionally associated with decreased survival. Furthermore, the two saturated FFAs, palmitate and stearate, induced TRAIL expression, triggered apoptosis, and inhibited proliferation in pancreatic cancer cells. These results, may open new therapeutic options for targeting pancreatic cancer.

Urinary metabolomics was explored using nuclear magnetic resonance (NMR) spectroscopy to investigate metabolomics profiles in the urine of PDAC patients. A distinct urinary metabolomics signature was found in urine of patients with newly diagnosed PDAC [52], which reliably could separate patients with PDAC and controls with benign disease. Of particular interest was the finding that the increased urinary metabolomic profile decreased after surgical R0 resection. The findings could point to a future "dip stick" test for pancreatic cancer, but further validation of these results is needed.

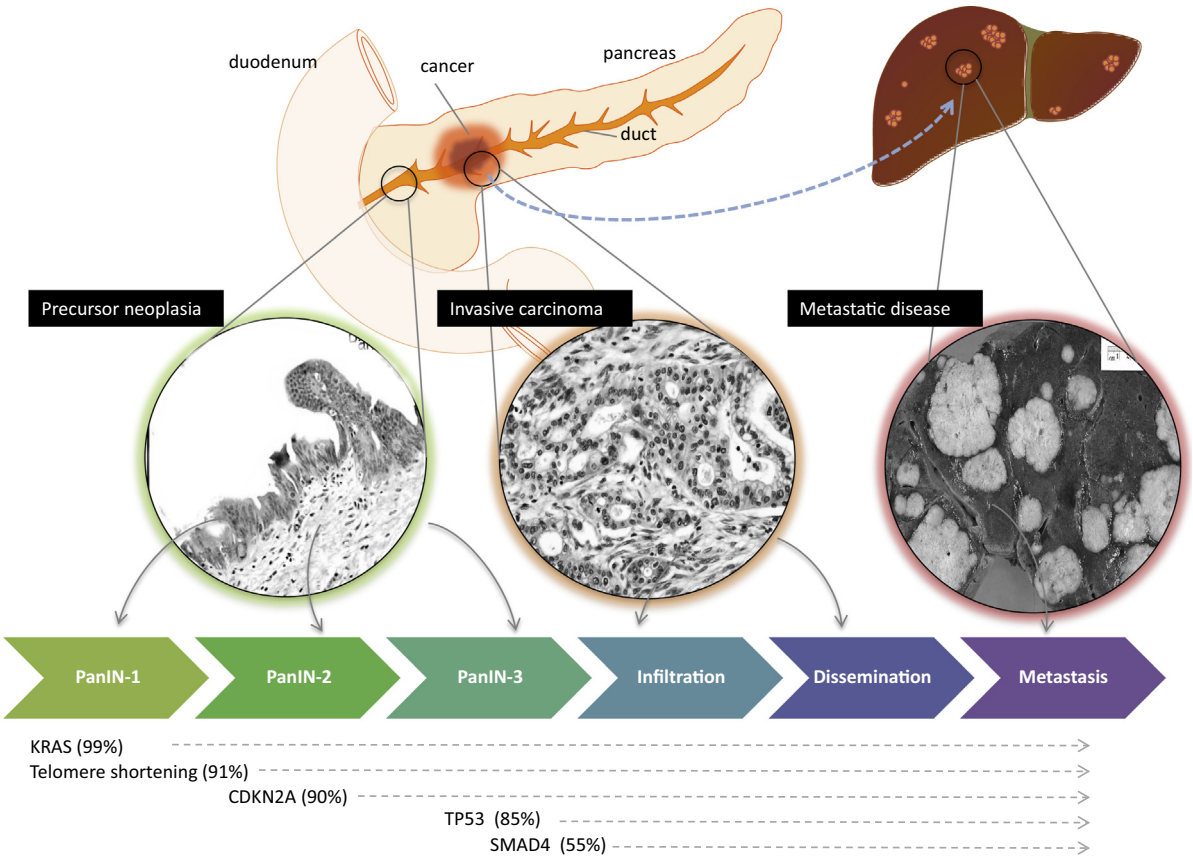

Fig. 1. Progression model in pancreatic ductal adenocarcinoma (PDAC). Depicted is the stepwise progression of pancreatic intraepithelial neoplasia (PanIN) with corresponding early and late genetic events typically found in the epithelial neoplastic cells.

While the metabolomics studies using different technology platforms and samples from various tissue types can provide further insight into cancer biology, the current challenge with the results is mainly the validity and reproducibility. Markers and panel appears to change across studies and technology, thus making it difficult to find anyone panel with a superior diagnostic, predictive or prognostic value over the other.

Evidence for change in cancer metabolism from animal studies

Several aspects of glycemic load and increased risk for pancreas cancer development stem from a number of animal studies. Notably, tumor maintenance relies on continued activity of driver oncogenes, although their rate-limiting role is highly context dependent. Oncogenic Kras mutation is the signature event in PDAC, serving a critical role in tumor initiation. The influence and control of *kras* by using mouse models for pancreatic cancer have been explored to a considerable degree [54–61]. Here we, present some of the recent findings pertaining to the influence of metabolomics.

For one, a delayed progression of pancreatic cancer occurs with caloric restriction in mice [57], indicating that restriction of nutrients or calories pose less metabolic stress on the pancreas. Adding proof to the concept, was a study in mice on high-fat diet that induced *kras* mutations and *cox-2*, which are known important genetic steps for pancreas cancer development [59]. These findings were replicated in another mouse-model of conditional *kras* activated mice, which demonstrated accelerated development of PanIN lesions with intake of a high-caloric, high-fat diet [55]. Furthermore, in an inducible *kras*-driven PDAC mouse model the transcriptome and metabolomic analyses indicated that *kras* appeared to be central in controlling tumor metabolism through stimulation of glucose uptake and channeling of glucose intermediates into the hexosamine biosynthesis and pentose phosphate pathways (PPP) [56]. The study provides mechanistic insights into how oncogenic *kras* advocates metabolic reprogramming in native tumors, and points to possible metabolic targets that can be exploited for therapeutic benefit in PDAC. Indeed, the search for the metabolic Achillees heel is what researchers look for in order to improve the current insufficient treatment options and response in PDAC [15]. Indeed, as kras is the driver of carcinogenesis it may also be the culprit lesion to target, as data suggest this process is autophagy dependent and thus amenable to potential intervention [15].

Metabolic genes, pathways and their variation to metabolic stress

Genetic variations in inflammatory response and insulin resistance may affect the risk of obesity- and diabetes-related pancreatic cancer [62], and in part also explain the diverting findings in some of the studies. Notably, inter-individual variation in metabolism/antioxidant genes could interact with dietary intake to influence pancreatic cancer risk [63]. Also, glucose metabolism gene polymorphisms may even affect clinical outcome in pancreatic cancer [64]. However, several pathways may be involved in the metabolic influence on cancer biology of which a few are mentioned.

As such, cancer cell metabolism differs from normal cells, yet the regulatory mechanisms responsible for these differences are incompletely understood, particularly in response to acute changes in the tumor microenvironment. The importance of the tumor-stroma interaction in pancreatic cancer is obvious through the strong desmoplastic reaction seen in most tumors and may be

a potential target for therapy. In one study [65] the "metabolic gene" expression profiles of primary and metastatic lesions from pancreatic cancer patients were analyzed by gene expression arrays. Metabolic genes involved in glycolysis, tri-carboxylic acid pathway, pentose-phosphate pathway and fatty acid metabolism were identified. Two distinct patterns emerged; firstly, genes that were either upregulated in primary and most of the metastatic lesions and, secondly, genes that were upregulated only in specific metastatic lesions and in a site-specific manner. Notably, a differential metabolic status of tumor and stromal components and elevation of aerobic glycolysis gene expression were found. This points to the importance of understanding mechanisms that may regulate (and as such represent potential targets for intervention) in this regard. One such potential mechanism may be found in the RNA-binding protein named HuR. HuR (or, a.k.a. human embryonic lethal abnormal vision-like protein; ELAVL) is a ubiquitously expressed protein that has been extensively investigated in cancer research [66]. HuR acts under acute stress to regulate core signaling-pathways in cancer through post-transcriptional regulation of mRNA targets. It has been shown [67], that HuR regulates the metabolic phenotype in pancreatic cancer cells and is critical for survival under acute glucose deprivation. HuR-proficient cells utilized less glucose, but produced greater lactate, as compared with HuR-deficient cells. Lactate is known to be a potent driver of cell survival and proliferation and even acts as an energy source in the tumor microenvironment [68]. Further, acute glucose deprivation was found to act as a potent stimulus for HuR translocation from the nucleus to the cytoplasm, where HuR stabilizes its mRNA targets. A gene expression array on ribonucleoprotein-immunoprecipitated mRNAs bound to HuR and identified 11 novel HuR target transcripts that encode enzymes central to glucose metabolism. Three (GPI, PRPS2 and IDH1) were selected for validation studies, and confirmed as genuine HuR targets. HuR is thus to be considered as a critical regulator of pancreatic cancer cell metabolism and survival under acute glucose deprivation [67]. However, while being potentially exploited as a therapy target [69–71], the HuR protein appears to have diverse functions in cancer that need to be better understood in advance [66,72].

Another example of signal transduction pathways that are activated when prone to metabolic stress is the release of so-called damage-associated molecular pattern molecules (DAMPs) that regulate cell death and cell survival [73]. The prototypical DAMP, high-mobility group box 1 protein (HMGB1), is released with sustained autophagy, late apoptosis and necrosis. HMGB1 protein triggers autophagy or apoptosis in cancer cells, depending on its redox status. Reducible HMGB1 binds to the receptor for advanced glycation end products (RAGE), induces Beclin 1-dependent autophagy and promotes pancreatic or colon tumor cell line resistance to chemotherapeutic agents or ionizing radiation. In contrast, oxidized HMGB1 increases the cytotoxicity of these agents and induces apoptosis via the mitochondrial pathway. This suggests a new function for HMGB1 within the tumor microenvironment, regulating cell death and survival and suggests that it plays an important functional role in cross-regulating apoptosis and autophagy. Recent results suggest that RAGE together with HMGB1 are required for optimal mitochondrial function within tumors. In their study [74], Kang et al. found RAGE present in mitochondria of cultured tumor cells and in primary tumors. RAGE and HMGB1 coordinately enhanced tumor cell mitochondrial complex I activity, ATP production, tumor cell proliferation and migration. Lack of RAGE or inhibition of HMGB1 release diminished ATP production and slowed tumor growth in vitro and in vivo. This points to a HMGB1-RAGE pathway with changes in bioenergetics in pancreas cancer. Clinically, higher levels of serum HMGB1 are associated with advanced disease and shorter survival [75] and soluble RAGE has been reported for monitoring response to chemotherapy [76].

Autophagy in pancreas cancer – good or bad?

Autophagy (programmed cell survival) is a metabolic process of lysosome-mediated self-digestion that promotes pancreatic cancer growth. Cells constantly weigh up signals from their environment against their own integrity and metabolic status and decide whether to live or die [77]. Such cell death decisions are central to the progression and treatment of cancer. The term autophagy describes the processes that deliver cytoplasmic macromolecules and organelles to lysosomes for degradation. Both inflammation and autophagy are cellular defense mechanisms. When these processes are deregulated (deficient or overactivated) they produce pathologic effects, such as oxidative stress, metabolic impairments, and cell death [78]. Unresolved inflammation and disrupted regulation of autophagy are common features of pancreatitis and pancreatic cancer. Furthermore, obesity promotes inflammation and inhibits or deregulates autophagy, creating an environment that facilitates the induction and progression of pancreatic cancer [78]. Although little is known about how inflammation, autophagy, and obesity interact to promote cancerogenesis, it appears that pancreatic cancers have a distinct dependence on autophagy (Fig. 2) through several mechanisms [33,79–86].

In a study of pancreatic cancer primary tumors and cell lines elevated autophagy was shown under basal conditions [83]. Genetic or pharmacologic inhibition of autophagy in vitro lead to increased reactive oxygen species (ROS), elevated DNA damage, and a metabolic defect leading to decreased mitochondrial oxidative phosphorylation – molecular changes that all result in growth suppression of pancreatic cancer cells. Notably, inhibition of autophagy by chloroquine (an anti-malaria drug used widely around the world) leads to tumor regression and longer survival in pancreatic cancer xenografts and in genetic mouse models [83]. It has been proposed that the effect of chloroquine and some other drugs, are mediated through a reactivation of TP53 [79]. However, in a study of mice containing oncogenic Kras and lacking p53 [85], the loss of autophagy did not block tumor progression, but rather accelerated cancer progression, with metabolic analysis revealing enhanced glucose uptake and enrichment of anabolic pathways, which can fuel tumor growth. As such, there appears to be a "yin-yang" role of autophagy in pancreatic cancer that is dependent on the presence of TP53 and the levels of RAGE [87], and one that needs to be taken into account when considering this as a target for therapy.

As chloroquine and its derivatives are potent inhibitors of autophagy and have been used safely in human patients for decades for other purposes, it may represent a novel area for targeted treatment. However, the exact mechanism is not known and needs to be further investigated. However, better understanding of autophagy as a mechanism for both tumor growth and tumor suppression is needed.

Glutamine pathway and hypoxia

Glutamine is an abundant and versatile nutrient that participates in energy formation, redox homeostasis, macromolecular synthesis, and signaling in cancer cells [88]. These characteristics make glutamine metabolism an appealing target for new clinical strategies to detect, monitor, and treat cancer [88]. In pancreatic cancer, the reprogramming of glutamine metabolism is mediated by oncogenic KRAS through the transcriptional upregulation and repression of key metabolic enzymes in this pathway [61]. Further, glutamine metabolism is changed in a pancreatic cancer cells,

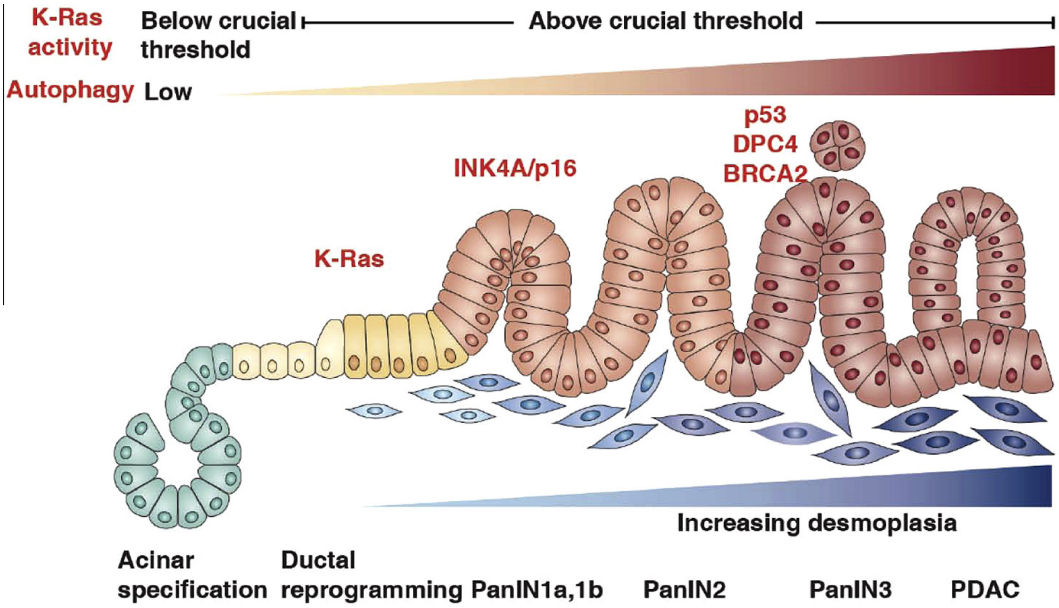

Fig. 2. KRAS mutation, autophagy and desmoplasia in pancreatic cancer progression. Simplified model detailing the relative contribution along the PanIN-progression model in ductal adenocarcinoma. Reproduced with permission under the Creative Commons Attribution Noncommercial License from Kang and Dang, Am J Cancer Res, 2012.

suggesting that glutamine is largely consumed as a nitrogen donor in nucleotide and amino acid biosynthesis [89]. Moreover, hypoxia increases the "glycolytic" switch of pancreatic cancer cells from oxidative phosphorylation to lactate production by several mechanisms [61,90,91]. The increased lactate efflux from hypoxic cancer cells favors the growth of normoxic cancer cells (suggesting that lactate is utilized as an energy source). Furthermore, glutamine metabolization by hypoxic pancreatic tumor cells is essential for cell survival and proliferation [91]. Metabolized glucose and glutamine converge toward a common pathway, termed hexosamine biosynthetic pathway, which allows modifications of proteins [91]. Also, mutated KRAS pancreas cancer cells have been shown to control tumor metabolism through stimulation of glucose uptake and channeling of glucose intermediates into the hexosamine biosynthesis and pentose the phosphate pathways (PPP). Thus, the essentiality of the KRAS pathway [58,61] in pancreatic cancer (knowing that it is dispensable in normal cells) may provide novel therapeutic approaches, yet the interplay with other key players, such as hypoxia-inducible factor (HIF-1alpha) and MUC1 warrants further investigation [12,90,91].

Conclusions and future direction

The genetic landscape of pancreatic cancer shows mutational inactivation in the critical gene set KRAS-CDKN2A-TP53-SMAD4 in the majority of adenocarcinomas. Yet, this knowledge has until now not provided new diagnostic or therapeutic advances that has revolutionized the outcome of cancer therapy. Targeting specific mechanism of cancer metabolism may allow for better tumor control and improved clinical outcomes for patients struck with this deadly disease. As cancer cells depend on certain metabolic pathways that provide for consistent energy deliverance for homeostasis and proliferation, such as glucose and glutamine, finding ways to block these nutrients, their associated pathways or target their molecular co-players may prove to be alternative strategies for future therapy. As pancreatic cancers rely on autophagy to progress and thrive, better understanding of the controlling mechanisms may provide additional targets for intervention. Indeed, while many of the pathways and mechanisms in cancer metabolism remains poorly understood [13,16], there is a growing knowledge and conceptual understanding for the potential in 'cutting the fuel' as a target for cancer control in the future [15].

Conflict of Interest

The authors have no conflicts of interest to disclose.

References

[1] K. Søreide, B. Aagnes, B. Møller, A. Westgaard, F. Bray, Epidemiology of pancreatic cancer in Norway: trends in incidence, basis of diagnosis and survival 1965–2007, Scand. J. Gastroenterol. 45 (2010) 82–92.
[2] C.L. Wolfgang, J.M. Herman, D.A. Laheru, et al., Recent progress in pancreatic cancer, CA Cancer J. Clin. 63 (2013) 318–348.
[3] A. Vincent, J. Herman, R. Schulick, R.H. Hruban, M. Goggins, Pancreatic cancer, Lancet 378 (2011) 607–620.
[4] S.J. Murphy, S.N. Hart, J.F. Lima, et al., Genetic alterations associated with progression from pancreatic intraepithelial neoplasia to invasive pancreatic tumor, Gastroenterology 145 (1098–109) (2013) e1.
[5] J.B. Koorstra, G. Feldmann, N. Habbe, A. Maitra, Morphogenesis of pancreatic cancer: role of pancreatic intraepithelial neoplasia (PanINs), Langenbeck Arch. Surg. 393 (2008) 561–570.
[6] C.A. Iacobuzio-Donahue, V.E. Velculescu, C.L. Wolfgang, R.H. Hruban, Genetic basis of pancreas cancer development and progression: insights from whole-exome and whole-genome sequencing, Clin. Cancer Res. 18 (2012) 4257–4265.
[7] A.V. Biankin, N. Waddell, K.S. Kassahn, et al., Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes, Nature 491 (2012) 399–405.
[8] S.E. Kern, C. Shi, R.H. Hruban, The complexity of pancreatic ductal cancers and multidimensional strategies for therapeutic targeting, J. Pathol. 223 (2011) 295–306.
[9] D.D. Von Hoff, T. Ervin, F.P. Arena, et al., Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine, New Engl. J. Med. 369 (2013) 1691–1703.
[10] K.P. Olive, M.A. Jacobetz, C.J. Davidson, et al., Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324 (2009) 1457–1461.
[11] M. Hidalgo, New insights into pancreatic cancer biology, Ann. Oncol. 23 (Suppl 10) (2012). pp. x135–8.
[12] G.L. Semenza, HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations, J. Clin. Invest. 123 (2013) 3664–3671.
[13] I. Regel, B. Kong, S. Raulefs, et al., Energy metabolism and proliferation in pancreatic carcinogenesis, Langenbeck Arch. Surg. 397 (2012) 507–512.
[14] S. Vasseur, R. Tomasini, R. Tournaire, J.L. Iovanna, Hypoxia induced tumor metabolic switch contributes to pancreatic cancer aggressiveness, Cancers (Basel) 2 (2010) 2138–2152.
[15] A. Le, N.V. Rajeshkumar, A. Maitra, C.V. Dang, Conceptual framework for cutting the pancreatic cancer fuel supply, Clin. Cancer Res. 18 (2012) 4285–4290.

[16] M.G. Vander Heiden, Exploiting tumor metabolism: challenges for clinical translation, J. Clin. Invest. 123 (2013) 3648–3651.
[17] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[18] L. Jiao, D. Li, Epidemiology and prospects for prevention of pancreatic cancer, in: J.P. Neoptolemos, R. Urrutia, J.L. Abbruzzese, M.W. Büchler (Eds.), Pancreatic Cancer, Springer, 2010, pp. 3–26.
[19] A.A. Arslan, K.J. Helzlsouer, C. Kooperberg, et al., Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan), Arch. Int. Med. 170 (2010) 791–802.
[20] S. Rohrmann, J. Linseisen, U. Nothlings, et al., Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition, Int. J. Cancer 132 (2013) 617–624.
[21] D.S. Michaud, A. Vrieling, L. Jiao, et al., Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan), Cancer Causes Control 21 (2010) 1213–1225.
[22] M. Obon-Santacana, N. Slimani, L. Lujan-Barroso, et al., Dietary intake of acrylamide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, Ann. Oncol. 24 (2013) 2645–2651.
[23] N. Bhoo-Pathy, C.S. Uiterwaal, V.K. Dik, et al., Intake of coffee, decaffeinated coffee, or tea does not affect risk for pancreatic cancer: results from the European Prospective Investigation into Nutrition and Cancer Study, Clin. Gastroenterol. Hepatol. 11 (2013) 1486–1492.
[24] S.C. Chuang, R. Stolzenberg-Solomon, P.M. Ueland, et al., A U-shaped relationship between plasma folate and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition, Eur. J. Cancer 47 (2011) 1808–1816.
[25] M. Leenders, S. Bhattacharjee, P. Vineis, et al., Polymorphisms in genes related to one-carbon metabolism are not related to pancreatic cancer in PanScan and PanC4, Cancer Causes Control 24 (2013) 595–602.
[26] V.A. Grote, S. Rohrmann, A. Nieters, et al., Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, Diabetologia 54 (2011) 3037–3046.
[27] B.M. Wolpin, Y. Bao, Z.R. Qian, et al., Hyperglycemia, insulin resistance, impaired pancreatic beta-cell function, and risk of pancreatic cancer, J. Nat. Can. Inst. 105 (2013) 1027–1035.
[28] J.W. Elena, E. Steplowski, K. Yu, et al., Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium, Cancer Causes Control 24 (2013) 13–25.
[29] H. Tang, P. Wei, E.J. Duell, et al., Genes-environment interactions in obesity- and diabetes-associated pancreatic cancer: a GWAS data analysis, Cancer Epidemiol. Biomarkers Prevent 23 (1) (2014) 98–106.
[30] D. Li, E.J. Duell, K. Yu, et al., Pathway analysis of genome-wide association study data highlights pancreatic development genes as susceptibility factors for pancreatic cancer, Carcinogenesis 33 (2012) 1384–1390.
[31] V.A. Grote, S. Rohrmann, L. Dossus, et al., The association of circulating adiponectin levels with pancreatic cancer risk: a study within the prospective EPIC cohort, Int. J. Cancer 130 (2012) 2428–2437.
[32] V.A. Grote, R. Kaaks, A. Nieters, et al., Inflammation marker and risk of pancreatic cancer: a nested case-control study within the EPIC cohort, Br. J. Cancer 106 (2012) 1866–1874.
[33] R. Kang, D. Tang, M.T. Lotze, H.J. Zeh 3rd., AGER/RAGE-mediated autophagy promotes pancreatic tumorigenesis and bioenergetics through the IL6-pSTAT3 pathway, Autophagy 8 (2012) 989–991.
[34] P.J. Vernon, H.J. Zeh Iii, M.T. Lotze, The myeloid response to pancreatic carcinogenesis is regulated by the receptor for advanced glycation end-products, Oncoimmunology 2 (2013) e24184.
[35] V.A. Grote, A. Nieters, R. Kaaks, et al., The associations of advanced glycation end products and its soluble receptor with pancreatic cancer risk: a case-control study within the prospective EPIC Cohort, Cancer Epidemiol. Biomarkers Prevent 21 (2012) 619–628.
[36] R.H. Hruban, N.V. Adsay, J. Albores-Saavedra, et al., Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions, Am. J. Surg. Pathol. 25 (2001) 579–586.
[37] A.M. Macgregor-Das, C.A. Iacobuzio-Donahue, Molecular pathways in pancreatic carcinogenesis, J. Surg. Oncol. 107 (2013) 8–14.
[38] A. Neesse, A. Hahnenkamp, H. Griesmann, et al., Claudin-4-targeted optical imaging detects pancreatic cancer and its precursor lesions, Gut 62 (2013) 1034–1043.
[39] A. Criscimanna, L.J. Duan, J.A. Rhodes, et al., PanIN-specific regulation of Wnt signaling by HIF2alpha during early pancreatic tumorigenesis, Cancer Res. 73 (2013) 4781–4790.
[40] J. Yu, A. Li, S.M. Hong, R.H. Hruban, M. Goggins, MicroRNA alterations of pancreatic intraepithelial neoplasias, Clin. Cancer Res. 18 (2012) 981–992.
[41] N. Remmers, J.M. Bailey, A.M. Mohr, M.A. Hollingsworth, Molecular pathology of early pancreatic cancer, Cancer Biomarkers 9 (2010) 421–440.
[42] P.K. Mazur, H. Einwachter, M. Lee, et al., Notch2 is required for progression of pancreatic intraepithelial neoplasia and development of pancreatic ductal adenocarcinoma, Proc. Natl. Acad. Sci. USA 107 (2010) 13438–13443.
[43] N. Sato, N. Fukushima, R.H. Hruban, M. Goggins, CpG island methylation profile of pancreatic intraepithelial neoplasia, Mod. Pathol. 21 (2008) 238–244.
[44] C.A. Iacobuzio-Donahue, Genetic evolution of pancreatic cancer: lessons learnt from the pancreatic cancer genome sequencing project, Gut 61 (2012) 1085–1094.
[45] S. Yachida, S. Jones, I. Bozic, et al., Distant metastasis occurs late during the genetic evolution of pancreatic cancer, Nature 467 (2010) 1114–1117.
[46] E.A. Collisson, A. Sadanandam, P. Olson, et al., Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy, Nat. Med. 17 (2011) 500–503.
[47] S. Urayama, W. Zou, K. Brooks, V. Tolstikov, Comprehensive mass spectrometry based metabolic profiling of blood plasma reveals potent discriminatory classifiers of pancreatic cancer, Rapid. Commun. Mass Spectrom. 24 (2010) 613–620.
[48] A.B. Leichtle, U. Ceglarek, P. Weinert, et al., Pancreatic carcinoma, pancreatitis, and healthy controls: metabolite models in a three-class diagnostic dilemma, Metabolomics 9 (2013) 677–687.
[49] T. Kobayashi, S. Nishiumi, A. Ikeda, et al., A novel serum metabolomics-based diagnostic approach to pancreatic cancer, Cancer Epidemiol. Biomarkers Prevent 22 (2013) 571–579.
[50] S.K. Vareed, V.B. Bhat, C. Thompson, et al., Metabolites of purine nucleoside phosphorylase (NP) in serum have the potential to delineate pancreatic adenocarcinoma, PloS one 6 (2011) e17177.
[51] G. Zhang, P. He, H. Tan, et al., Integration of metabolomics and transcriptomics revealed a fatty acid network exerting growth inhibitory effects in human pancreatic cancer, Clin. Cancer Res. 19 (2013) 4983–4993.
[52] V.W. Davis, D.E. Schiller, D. Eurich, O.F. Bathe, M.B. Sawyer, Pancreatic ductal adenocarcinoma is associated with a distinct urinary metabolomic signature, Ann. Surg. Oncol. 20 (Suppl 3) (2013). pp. S415–23.
[53] C. Napoli, N. Sperandio, R.T. Lawlor, A. Scarpa, H. Molinari, M. Assfalg, Urine metabolic signature of pancreatic ductal adenocarcinoma by (1)h nuclear magnetic resonance: identification, mapping, and evolution, J. Proteom. Res. 11 (2012) 1274–1283.
[54] T. Al Saati, P. Clerc, N. Hanoun, et al., Oxidative stress induced by inactivation of TP53INP1 cooperates with KrasG12D to initiate and promote pancreatic carcinogenesis in the murine pancreas, Am J. Pathol. 182 (2013) 1996–2004.
[55] D.W. Dawson, K. Hertzer, A. Moro, et al., High-fat, high-calorie diet promotes early pancreatic neoplasia in the conditional KrasG12D mouse model, Cancer Prev. Res. 6 (2013) 1064–1073.
[56] H. Ying, A.C. Kimmelman, C.A. Lyssiotis, et al., Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism, Cell 149 (2012) 656–670.
[57] S. Lanza-Jacoby, G. Yan, G. Radice, C. LePhong, J. Baliff, R. Hess, Calorie restriction delays the progression of lesions to pancreatic cancer in the LSL-KrasG12D; Pdx-1/Cre mouse model of pancreatic cancer, Exp. Biol. Med. (Maywood, NJ) 238 (2013) 787–797.
[58] B. Kong, C. Qia, M. Erkan, J. Kleeff, C.W. Michalski, Overview on how oncogenic Kras promotes pancreatic carcinogenesis by inducing low intracellular ROS levels, Frontiers Physiol. 4 (2013) 246.
[59] B. Philip, C.L. Roland, J. Daniluk, et al., A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice, Gastroenterology 145 (2013) 1449–1458.
[60] M.A. Shields, K. Ebine, V. Sahai, et al., Snail cooperates with KrasG12D to promote pancreatic fibrosis, Mol. Cancer Res. 11 (2013) 1078–1087.
[61] J. Son, C.A. Lyssiotis, H. Ying, et al., Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway, Nature 496 (2013) 101–105.
[62] H. Tang, P. Wei, E.J. Duell, et al., Genes-environment interactions in obesity- and diabetes-associated pancreatic cancer: a GWAS data analysis, Cancer Epidemiol. Biomarkers Prevent. 23 (2014) 98–106.
[63] R.J. Jansen, D.P. Robinson, R.Z. Stolzenberg-Solomon, et al., Polymorphisms in metabolism/antioxidant genes may mediate the effect of dietary intake on pancreatic cancer risk, Pancreas 42 (2013) 1043–1053.
[64] X. Dong, H. Tang, K.R. Hess, J.L. Abbruzzese, D. Li, Glucose metabolism gene polymorphisms and clinical outcome in pancreatic cancer, Cancer 117 (2011) 480–491.
[65] N.V. Chaika, F. Yu, V. Purohit, et al., Differential expression of metabolic genes in tumor and stromal components of primary and metastatic loci in pancreatic adenocarcinoma, PloS one 7 (2012) e32996.
[66] J. Wang, Y. Guo, H. Chu, Y. Guan, J. Bi, B. Wang, Multiple functions of the rna-binding protein HuR in cancer progression, treatment responses and prognosis, Int. J. Mol. Sci. 14 (2013) 10015–10041.
[67] R.A. Burkhart, D.M. Pineda, S.N. Chand, et al., HuR is a post-transcriptional regulator of core metabolic enzymes in pancreatic cancer, RNA Biology 10 (2013) 1312–1323.
[68] J.R. Doherty, J.L. Cleveland, Targeting lactate metabolism for cancer therapeutics, J. Clin. Invest. 123 (2013) 3685–3692.
[69] W. Al-Ahmadi, M. Al-Ghamdi, N. Al-Souhibani, K.S. Khabar, MiR-29a inhibition normalizes HuR over-expression and aberrant AU-rich mRNA stability in invasive cancer, J. Pathol. 230 (2013) 28–38.
[70] Y.C. Cheng, J.P. Liou, C.C. Kuo, et al., MPT0B098, a novel microtubule inhibitor that destabilizes the hypoxia-inducible factor-1alpha mRNA through decreasing nuclear-cytoplasmic translocation of RNA-binding protein HuR, Mol. Cancer Ther. 12 (2013) 1202–1212.
[71] P.C. Chu, H.C. Chuang, S.K. Kulp, C.S. Chen, The mRNA-stabilizing factor HuR protein is targeted by beta-TrCP protein for degradation in response to glycolysis inhibition, J. Biol. Chem. 287 (2012) 43639–43650.

[72] C. von Roretz, X.J. Lian, A.M. Macri, et al., Apoptotic-induced cleavage shifts HuR from being a promoter of survival to an activator of caspase-mediated apoptosis, Cell Death Differen. 20 (2013) 154–168.
[73] D. Tang, M.T. Loze, H.J. Zeh, R. Kang, The redox protein HMGB1 regulates cell death and survival in cancer treatment, Autophagy 6 (2010) 1181–1183.
[74] R. Kang, D. Tang, N.E. Schapiro, et al., The HMGB1/RAGE inflammatory pathway promotes pancreatic tumor growth by regulating mitochondrial bioenergetics, Oncogene 33 (2014) 567–577.
[75] H.W. Chung, J.B. Lim, S. Jang, K.J. Lee, K.H. Park, S.Y. Song, Serum high mobility group box-1 is a powerful diagnostic and prognostic biomarker for pancreatic ductal adenocarcinoma, Cancer Sci. 103 (2012) 1714–1721.
[76] C. Wittwer, S. Boeck, V. Heinemann, et al., Soluble receptor of advanced glycation end products (sRAGE) indicates response to chemotherapy in pancreatic cancer patients, Int. J. Clin. Pharmacol. Ther. 51 (2013) 67–69.
[77] R.L. Macintosh, K.M. Ryan, Autophagy in tumour cell death, Sem. Cancer Biol. 23 (2013) 344–351.
[78] I. Gukovsky, N. Li, J. Todoric, A. Gukovskaya, M. Karin, Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer, Gastroenterology 144 (1199–209) (2013) e4.
[79] C. Fiorini, M. Menegazzi, C. Padroni, et al., Autophagy induced by p53-reactivating molecules protects pancreatic cancer cells from apoptosis, Apoptosis 18 (2013) 337–346.
[80] T. Hamidi, C.E. Cano, D. Grasso, et al., NUPR1 works against the metabolic stress-induced autophagy-associated cell death in pancreatic cancer cells, Autophagy 9 (2013) 95–97.
[81] S. Yang, A.C. Kimmelman, A critical role for autophagy in pancreatic cancer, Autophagy 7 (2011) 912–913.
[82] S. Fujii, S. Mitsunaga, M. Yamazaki, et al., Autophagy is activated in pancreatic cancer cells and correlates with poor patient outcome, Cancer Sci. 99 (2008) 1813–1819.
[83] S. Yang, X. Wang, G. Contino, et al., Pancreatic cancers require autophagy for tumor growth, Gene Dev. 25 (2011) 717–729.
[84] V. Rausch, L. Liu, A. Apel, et al., Autophagy mediates survival of pancreatic tumour-initiating cells in a hypoxic microenvironment, J. Pathol. 227 (2012) 325–335.
[85] M.T. Rosenfeldt, J. O'Prey, J.P. Morton, et al., P53 status determines the role of autophagy in pancreatic tumour development, Nature 504 (2013) 296–300.
[86] R. Kang, D. Tang, Autophagy in pancreatic cancer pathogenesis and treatment, Am. J. Cancer Res. 2 (2012) 383–396.
[87] R. Kang, D. Tang, N.E. Schapiro, et al., The receptor for advanced glycation end products (RAGE) sustains autophagy and limits apoptosis, promoting pancreatic tumor cell survival, Cell Death Differen. 17 (2010) 666–676.
[88] C.T. Hensley, A.T. Wasti, R.J. DeBerardinis, Glutamine and cancer: cell biology, physiology, and clinical opportunities, J. Clin. Invest. 123 (2013) 3678–3684.
[89] W. Zhou, M. Capello, C. Fredolini, et al., Proteomic analysis reveals Warburg effect and anomalous metabolism of glutamine in pancreatic cancer cells, J. Proteom. Res. 11 (2012) 554–563.
[90] N.V. Chaika, T. Gebregiworgis, M.E. Lewallen, et al., MUC1 mucin stabilizes and activates hypoxia-inducible factor 1 alpha to regulate metabolism in pancreatic cancer, Proc. Natl. Acad. Sci. USA 109 (2012) 13787–13792.
[91] F. Guillaumond, J. Leca, O. Olivares, et al., Strengthened glycolysis under hypoxia supports tumor symbiosis and hexosamine biosynthesis in pancreatic adenocarcinoma, Proc. Natl. Acad. Sci. USA 110 (2013) 3919–3924.