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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

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