Pancreatology 12 (2012) 344–349

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Review article

The burning question: Why is smoking a risk factor for pancreatic cancer?

Stephen J. Pandol [a], Minoti V. Apte [b], Jeremy S. Wilson [b], Anna S. Gukovskaya [a], Mouad Edderkaoui [a,*]

[a] Veterans Affairs Greater Los Angeles Healthcare System, University of California Los Angeles, CA, USA
[b] Pancreatic Research Group, South Western Sydney Clinical School, University of New South Wales, Sydney, New South Wales, Australia

ARTICLE INFO

Article history:
Received 29 March 2012
Received in revised form
13 June 2012
Accepted 29 June 2012

Keywords:
Smoking
Pancreatic cancer
Fibrosis
Inflammation

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease. The prognosis is poor; less than 5% of those diagnosed are still alive five years after diagnosis, and complete remission is still rare. Tobacco smoking is a major risk factor of pancreatic cancer. However, the mechanism(s) through which it causes the disease remains unknown. Accumulating evidence indicates that carcinogenic compounds in cigarette smoke stimulate pancreatic cancer progression through induction of inflammation and fibrosis which act in concert with genetic factors leading to the inhibition of cell death and stimulation of proliferation resulting in the promotion of the PDAC.

1. Pancreatic ductal adenocarcinoma: epidemiology and risk factors

1.1. Introduction

In the United States, over 40,000 individuals are diagnosed with pancreatic ductal adenocarcinoma (PDAC) and 37,000 die of the disease each year. The prognosis is poor with a 5 year survival of less than 5% [1]. Even with combinations of treatment (surgery, chemotherapy, radiotherapy) the outcome for patients with this disease remains dismal. The economic impact of the disease is also of great concern as the total costs of the disease in the US are estimated to be $4.9 billion annually [2].

Over the past 5 years, there have been 10 negative Phase III trials investigating the effects of systemic treatment of advanced pancreatic cancer with chemotherapeutic agents [3,4]. The failure of these trials likely reflects our limited knowledge of pancreatic cancer biology, particularly with regard to the initiation and progression of the disease. Indeed, very little is known about how PDAC risk factors promote carcinogenesis.

Among the important risk factors for PDAC are chronic pancreatitis and diabetes mellitus. Chronic pancreatitis increases the risk of pancreatic cancer by up to 13 times [5,6]. Diabetes mellitus increases the risk by at least 2 times and the more recent the onset of diabetes the stronger the correlation with pancreatic cancer [7,8]. Aging, heavy alcohol drinking, family history of the disease, male gender and African American ethnicity are other risk factors for pancreatic cancer [9].

The major environmental and the strongest avoidable risk factor for pancreatic cancer is tobacco smoking (vide infra for detailed discussion) [10,11]. However, the pro-carcinogenic effects of smoking on the pancreas are inadequately studied. The goal of this review is to summarize information available on the pro-carcinogenic effects of smoking and underlying mechanisms; and to outline a research strategy designed to reveal the mechanisms through which smoking predisposes to PDAC.

1.2. PDAC characteristics: role of genetic alterations, inflammation and fibrosis

PDAC presents all classical hallmarks of cancer including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing

Abbreviations: cAMP, cyclic AMP; EGFR, epidermal growth factor receptor; ECM, extracellular matrix protein; IL-1β, interleukin 1 beta; MIP-1α, macrophage inflammatory protein 1 alpha; MMPs, matrix metalloproteinases; nAChRs, nicotinic acetylcholine receptors; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NNAA, 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal); NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta.

* Corresponding author. Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Blvd., Bldg 258, Rm. 340, Los Angeles, CA 90073, USA. Tel.: +1 310 478 3711x48545; fax: +1 310 268 4578.
E-mail address: medderkaoui@mednet.ucla.edu (M. Edderkaoui).

1424-3903/$ – see front matter
http://dx.doi.org/10.1016/j.pan.2012.06.002

angiogenesis and activating invasion and metastasis resulting from genetic alterations developed during the progression of the disease from pre-malignant lesions to the PDAC stage [12]. The somatic Kras mutation remains the major genetic mutation present in 90% of patients and perhaps the earliest genetic alteration associated with pancreatic cancer [13]. Kras mutation leads to the activation of downstream proliferative signaling such as the BRAF/MEK/Erk-mediated proliferation and survival pathway. The pro-oncogenic effects of Kras are enhanced by inactivating somatic mutations of multiple tumor suppressor genes including p53, MADH4, P16, and BRCA2 which are present in the human tumors. These multiple genetic mutations are involved in proliferation, resistance to cell death, and metastasis.

While the role of genetic mutations in carcinogenesis has been a widely accepted concept for several decades, it is only in the recent past that the key influence of the micro-environment on tumor growth and spread has been recognized and acknowledged [12,14,15]. Thus, inflammation and fibrosis, two major features of the stroma of pancreatic cancer are receiving increasing attention with regard to their effects on tumor behavior. It has been shown that acute necro-inflammation of the pancreas speeds up and promotes PDAC formation in mice containing pancreas-specific transgenes expressing Kras [16]. Progression to the PDAC stage in Kras mice subjected to pancreatitis is mediated at least, in part, by pro-survival transcription factor STAT3 which induces matrix metalloproteinase 7 (MMP7) expression [17]. STAT3 binding activity is increased by inflammatory cytokines known to be up-regulated during acute pancreatitis. Matrix metalloproteinases (MMPs) are important players in local invasion of cancer as well as angiogenesis and metastasis.

As noted earlier, PDAC is characterized by a prominent, dense desmoplastic reaction that surrounds the often scarce cancer cell clusters. One report showed that more extensive fibroblastic cell proliferation in PDAC correlated with poorer disease outcome [18]. The key producer of the cancer desmoplasia is the pancreatic stellate cell (PSC), a cell type now established as the central player in pancreatic fibrogenesis. In normal pancreas, PSCs are in an inactive or quiescent state. During pancreatic injury such as chronic pancreatitis and pancreatic cancer, PSCs are activated to a myofibroblastic state [19,20] resulting in synthesis of excessive amounts of extracellular matrix (ECM) proteins causing pathological fibrosis. *In vitro* and *in vivo* studies showed that PSCs play a major role in facilitating local growth and distant spread of pancreatic cancer [21–23]. The cells interact closely with cancer cells, inhibiting cancer cell apoptosis but promoting cancer cell proliferation, migration, invasion, and anchorage independent growth [21]. In turn, cancer cells induce PSC proliferation, activation and migration. PSCs also interact with endothelial cells to promote angiogenesis [23]. Interestingly, PSCs from the primary tumor have also been shown to travel to distant metastatic sites where they probably facilitate the seeding and growth of circulating cancer cells [23]. Recent studies have also implicated PSCs in both chemoresistance [24] and resistance to radiotherapy [25] (both well-known features of pancreatic cancer).

The factors mediating the interactions between PSCs and cancer cells and PSCs and endothelial cells are being increasingly identified. One mechanism through which activated stellate cells support cancer cells is through secretion of ECM proteins (collagen, fibronectin and laminin), MMPs and growth factors such as transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF). Both ECM proteins and growth factors promote survival of the cancer cells through activation of intracellular reactive oxygen species (ROS) generating systems in the pancreatic cancer cells such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes [26–29]. Activation of NADPH oxidase by growth factors also occurs in PSCs and their hepatic counterparts, hepatic stellate cells during the process of stellate cell activation [30,31]. Thus, oxidant stress is an important factor in desmoplasia and tumor growth in pancreatic cancer [21,32].

Fig. 1 summarizes and illustrates the three major contributors to pancreatic carcinogenesis: genetic mutations, inflammation and fibrosis. They act synergistically. Both cancer and stellate cells stimulate each other through secretion of TGF-β and PDGF by the cancer cells; or by secretion of extracellular matrix proteins such as collagen, fibronectin and laminin, growth factors, and MMPs by stellate cells. ECM proteins stimulate NADPH oxidase activity and ROS production, proliferation and resistance to death. MMPs facilitate invasion and metastasis. Cytokines and chemokines produced by the inflammatory cells promote Kras-induced proliferation and stimulate activation of stellate cells resulting in fibrosis. Both cancer and stellate cells interact with endothelial cells to promote new blood vessel formation, thereby facilitating metastasis.

1.3. Animal models of PDAC

The development of the genetic mouse models of PDAC has significantly advanced our understanding of the possible mechanisms mediating the initiation of this disease. These models are based for the most part on pancreatic acinar cell-specific activation of Kras. Most of them develop pre-invasive pancreatic neoplastic lesions called pancreatic intraepithelial neoplasms (PanINs) similar to ones found in the human disease [33]. However, most models of PanINs do not progress spontaneously to the PDAC stage of invasive and metastatic adenocarcinoma. Only three Kras models: Pdx1-Cre;LSL-Kras model [34], p48Cre;LSL-Kras [34], and EL-CreERT cLGL-Kras, fully replicate advanced PDAC phenotype including invasion, metastasis and fibrosis. Furthermore, a recent study showed that the extent of Kras activation determines PDAC induction, i.e., Kras mutation expression at a low level is not sufficient to trigger PDAC, whereas, higher levels of Kras expression result in advanced PDAC [35]. On the other hand, combinations of Kras activating mutation with other genetic alterations characteristic for PDAC, such as p53 inactivating mutations speed up and promote the PDAC development in mice. These data strongly indicate that Kras activation is necessary but not sufficient to develop PDAC; and suggest contribution of other cancer promoting factors acting in concert with Kras.

2. Tobacco smoking and pancreatic cancer

2.1. Epidemiology

More than 400,000 people die each year in the United States alone as a result of past or current cigarette smoking; adult smokers lose an average 13–15 years of life-expectancy because of their smoking [36,37]. In addition to regular cigarettes and cigars, other forms of tobacco include smokeless tobacco (also called chewing tobacco, snuff and snus), pipes and hookahs (water-pipes). Although most research has focused on the harms of cigarette smoking, all forms of tobacco are harmful. Importantly, both smokeless tobacco and smoking tobacco are known to cause cancer in humans. Lung cancer is by far the first and most studied tobacco-related cancer. In addition to PDAC, other tobacco-related cancers include, tongue, larynx, stomach and brain cancers [12,13]. 80%–90% of lung cancer patients in the United States involve smoking [38]. In general, for people who have already developed cancer, quitting smoking reduces the risk of developing a second cancer [39–41].