Biochimica et Biophysica Acta 1856 (2015) 13–27

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Recent advances in pancreatic cancer: biology, treatment, and prevention

Divya Singh [a], Ghanshyam Upadhyay [a,*], Rakesh K. Srivastava [b,*], Sharmila Shankar [b,c,**]

[a] Department of Biology, City College of New York, 160 Convent Avenue, New York, NY 10031, USA
[b] Kansas City VA Medical Center, 4801 Linwood Boulevard, Kansas City, MO 64128, USA
[c] Department of Pathology, School of Medicine, University of Missouri-Kansas City, Kansas City, MO 64108, USA

ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 28 April 2015
Accepted 30 April 2015
Available online 11 May 2015

Keywords:
Pancreatic cancer
Cancer stem cell
Signaling pathways
Cancer prevention
Natural Product

ABSTRACT

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in United States. Efforts have been made towards the development of the viable solution for its treatment with constrained accomplishment because of its complex biology. It is well established that pancreatic cancer stem cells (CSCs), albeit present in a little count, contribute incredibly to PC initiation, progression, and metastasis. Customary chemo and radiotherapeutic alternatives, however, expands general survival, the related side effects are the significant concern. Amid the most recent decade, our insight about molecular and cellular pathways involved in PC and role of CSCs in its progression has increased enormously. Presently the focus is to target CSCs. The herbal products have gained much consideration recently as they, usually, sensitize CSCs to chemotherapy and target molecular signaling involved in various tumors including PC. Some planned studies have indicated promising results proposing that examinations in this course have a lot to offer for the treatment of PC. Although preclinical studies uncovered the importance of herbal products in attenuating pancreatic carcinoma, limited studies have been conducted to evaluate their role in clinics. The present review provides a new insight to recent advances in pancreatic cancer biology, treatment and current status of herbal products in its anticipation.

Contents

Abbreviations: Oct4, octamer-binding transcription factor 4; ABCG2, ATP-binding cassette sub-family G member 2; CXCR4, C-X-C chemokine receptor type 4; FGF, fibroblast growth factor; Frizzled-9, frizzled class receptor 9; Glut1, glucose transporter 1; Foxa2, forkhead box A2; Sox2, sex determining region Y box 2; Klf4, kruppel like factor 4; c-Myc, v-Myc avian myelocytomatosis viral oncogene homolog; FGF, fibroblast growth factor; ESA, epithelial-specific antigen; ALDH1, acetaldehyde dehydrogenases 1; ABCB1, ATP-binding cassette sub-family B member 1; MDR1, multidrug resistance protein 1; DCLK1, doublecortin-like kinase 1; Cdkn2a, cyclin-dependent kinase inhibitor 2a; Dpc4 or Smad4, deleted in pancreatic carcinoma, locus 4; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor α; MCP-1, monocyte chemotactic protein-1; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; PDGF, platelet-derived growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF-β, transforming growth factor beta; Chk2, checkpoint kinase 2; COX-2, cyclooxygenase-2; IGF-1R, insulin-like growth factor-1 receptor; VEGF, vascular endothelial growth factor; HIF1α, hypoxia inducible factor 1α; MMP, matrix metalloproteinase, TWIST1, Twist-related protein 1; ICAM1, intercellular adhesion molecule 1; Bcl-2, B-cell lymphoma 2, Bcl-xL, B-cell lymphoma extra-large, Bad, Bcl-2-associated death promoter; Bak, Bcl-2 homologous antagonist/killer; Bax, Bcl-2-associated X protein; Mcl-1, induced myeloid leukemia cell differentiation protein; Pdx1, pancreatic and duodenal homeobox 1, uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; MAPK, mitogen activated protein kinase; FoxO1, forkhead box O1; FoxO3, forkhead box O3; PI3K, phosphatidylinositol 3-kinase; PARP, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homolog; PDGFRα, alpha-type platelet-derived growth factor receptor; IGF2R, insulin-like growth factor 2 receptor; ENG, endoglin, ALK1, activin receptor-like kinase 1; FKHRL1, forkhead box O3a; FKHR, forkhead box O1; AFX, forkhead box O4; TP53, tumor protein p53; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Cdk4, cyclin-dependent kinase 4; Raf-1, RAF proto-oncogene serine/threonine-protein kinase; Her-2, human epidermal growth factor receptor 2; EMT, endothelial to meseanchymal transition; DR, death receptor; EpCAM, epithelial cell adhesion molecule; vWF, von Willebrand factor; PCNA, proliferating cell nuclear antigen; Hsp, heat shock potein; XIAP, X-linked inhibitor of apoptosis protein; IAP, inhibitor of apoptosis protein; Pdk1, phosphoinositide-dependent kinase-1; mTOR, mammalian target of rapamycin; ERK, extracellular-signal-regulated kinases; JNK, c-Jun N-terminal kinases; HDAC, histone deacetylases; p38, P38 mitogen-activated protein kinases; ROS, reactive oxygen species

* Corresponding author.
** Correspondence to: S. Shankar, Kansas City VA Medical Center, 4801 Linwood Boulevard, Kansas City, MO 64128.
E-mail addresses: divyasingh28sep@gmail.com (D. Singh), upadhyayiitr@gmail.com (G. Upadhyay), rsrivastava.lab@gmail.com (R.K. Srivastava), sharmila.shankar@va.gov (S. Shankar).

http://dx.doi.org/10.1016/j.bbcan.2015.04.003
0304-419X/

1. Introduction

The burden of pancreatic cancer (PC) has continuously increased worldwide. It is a serious health concern and fourth leading cause of cancer-related death in United States of America [1,2]. PC is described as a type of gastrointestinal tumor with a poor anticipation and a high level of danger and death rate [3]. More than 90% of pancreatic tumors have inception from the ductal epithelium of pancreas consequently termed as pancreatic ductal adenocarcinoma (PDAC). It is disturbing to see that frequency rate of the pancreatic tumor is relentlessly expanding in the western world [4]. The danger components for pancreatic cancer incorporate smoking, obesity and high utilization of processed meat. Age is positively correlated with pancreatic cancer incidences, and the larger part of cases are diagnosed over the age of 60 [5]. The introductory indications of patients with PDAC are back agony and dyspepsia with additional disturbing manifestations like the new onset of diabetes, jaundice, unconstrained profound vein thrombosis and weight reduction. When one begins perceiving, the tumor typically, spreads to the encompassing tissues or distant organs. For the tumors spotted in the head region of pancreas, the determination is actually productive and they are diagnosed relatively early because of biliary impediment. Nonetheless, the tumors in the body and tail of pancreas regularly stay asymptomatic until late in disease stage. Most of the patients (~80%) are identified with unresectable locally advanced or metastatic stage and the major cause is the delayed diagnosis and lack of specific blood or urine biomarkers to identify patients with increased risk of developing pancreatic cancer [6–9]. The routine diagnostics incorporate transabdominal ultrasound in the introductory assessment of the jaundiced patient alongside computed tomography (CT) scan or magnetic resonance imaging (MRI).

Despite the fact that the survival rate for most cancers has been increased lately in a couple of decades, little change is seen in the case of pancreatic cancer. The usual survival rate for pancreatic cancer patients is under six months, and just 3% patients survive over 5-years [6–9]. The reason is attributed to various factors including silent nature in early stages, aggressive tumor biology, the low scope of surgical management, and lack of effective systemic therapies. Although, the current procedures including surgery, chemotherapy, radiation, and immunosuppressants, have made great advances in diminishing tumor frequencies and death rates, pancreatic cancer remains a continuing challenge to the researchers. The treatment strategies at present utilized are not very encouraging [10]. There are exceptionally poor post-surgery survival rates even when the pancreatic tumor is surgically resected. Safety concerns related with these medications/techniques are likewise a significant issue for their accomplishment in the treatment of the disease [6–9]. The prevalent chemotherapeutic choices for the cancer treatment prolong the life of pancreatic cancer patients minimally, and the survival span in a large portion of the cases is not over one year. Since limited treatment choices are accessible, and it additionally shows resistance against chemo- and radiotherapies, it is important to find novel and viable methodologies for the treatment of pancreatic cancer [10].

Although the potential use of herbal components for the protection against various cancers began several decades ago, studies to understand the mechanism of their action at biochemical, genomic, and proteomic levels started very recently. Many plant products, such as triterpenes, flavonoids or polyphenols, are now established potent chemopreventive agents [11–15]. The phenolic substances are isolated from the wide range of vascular plants and have the ability to reduce and scavenge free radicals [16,17]. Epidemiological studies have shown the reduced risk of pancreatic cancer by increased consumption of fruits and vegetables [18]. In the recent past, a number of preclinical studies have demonstrated various degrees of the efficacy of herbal products both in vitro and in vivo [18]. Certain dietary agents, for example, resveratrol and curcumin, have been demonstrated to potentiate the standard chemotherapy [18]. It has been observed that herbal products target different pathways simultaneously therefore any solution including these products may be a smart thought for better results. Many groups are working in this direction, and the outcomes are promising towards the improvement of new helpful cure. In this review, we will examine the biology of the pancreatic tumor, diagnosis, treatment techniques and clinical trials. We will likewise concentrate on the plausible role of herbal products, alone or in combination with systemic chemopreventive medications, in the treatment of the pancreatic tumor.

2. Biology of pancreatic cancer

The biology of pancreatic cancer is perplexing and inadequately caught on. Pancreas has both exocrine and endocrine cells that can structure tumors; however, the likelihood is more for exocrine cells. The vast majority of the exocrine tumors are adenocarcinomas that begin in organ cells in the ductal epithelium and advances from premalignant injuries to the entirely invasive tumor. Tumors of the endocrine pancreas, commonly termed as islet cell tumors or neuroendocrine tumors, are less common and can be characterized into gastrinomas, insulinomas, glucagonomas, somatostatinomas, VIPomas, PPomas and so forth.

The microenvironment of the pancreatic tumor is made out of a few components, for example, pancreatic cancer cells, pancreatic cancer stem cells (pancreatic CSCs), and the thick, ineffectively vascularized stroma. The studies suggest that the stroma likewise regulate the