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# Investigating the role of transcription factors of pancreas development in pancreatic cancer

Ahmad Abu Turab Naqvi [a], Gulam Mustafa Hasan [b], Md Imtaiyaz Hassan [a, *]

[a] Center for Interdisciplinary Research in Basic Science, Jamia Millia Islamia, Jamia Nagar, New Delhi, 110025, India
[b] Department of Biochemistry, College of Medicine, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

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ABSTRACT

Pancreatic cancer (PC) is the seventh most common cause of cancer-related deaths worldwide that kills more than 300,000 people every year. Prognosis of PC is very poor with a five-year survival rate about 5%. The most common and highly observed type of PC is pancreatic ductal adenocarcinoma (PDAC). It is preceded by the progression of precursor lesions such as Pancreatic Intraepithelial Neoplasia (PanIN), Intraductal Papillary Neoplasm (IPMN) and Mucinous Cystic Neoplasm (MCN). PanIN is the most common among these premalignant lesions. Genes orchestrating the origin and differentiation of cells during organogenesis have the tendency to produce tumor cells in response to activating or inactivating mutations. Based on the following premise, we discuss the role of transcription factors (TFs) of pancreas development and cell fate differentiation in PC. Pancreas/duodenum homeobox protein 1 (PDX1), Pancreas transcription factor 1 subunit alpha (PTF1A), Nuclear receptor subfamily 5 group A member 2 (NR5A2), Hepatocyte nuclear factor 1-alpha (HNF1A) and Hepatocyte nuclear factor 1-beta (HNF1B) play vital role in the development and differentiation of pancreatic precursor cells. Mutated KRAS induces abnormalities in the regular function of these TFs which in turn cause abnormal cell growth and proliferation that leads to cancer. Thus, these TFs are highly susceptible for the origin of PC. Therefore, we propose that these TFs can be treated as therapeutic targets for the development of anticancer drugs.


## Introduction

Pancreas is an essential part of the gastrointestinal glandular system of the human physiology. It is made up of acinar cells that secrete a digestive enzyme, ductal cells secreting bicarbonate, centroacinar cells, endocrine islets and inactive stellate cells. It is an organ of endodermal derivation which regulates the digestion of proteins and carbohydrates along with controlling glucose homeostasis. Anatomically, it is differentiated into endocrine and exocrine parts that make 20% and 80% of the pancreas respectively. The exocrine part is made up of acinar and duct cells whereas endocrine pancreas comprises 'Islets of Langerhans'. These islets act as a hormone secreting machinery of the pancreas providing insulin, glucagon, and somatostatin to bloodstream [1,2].

The majority of pancreas neoplasms belongs to malignant cancers. Malignant cancer has the tendency to spread and invade nearby tissues ensuing metastasis. Furthermore, majority of pancreatic cancers (PCs) are adenocarcinomas that arise in the epithelial cell types. Adenocarcinomas are specific to glandular tissues. The other types of PCs that are relatively less frequent are neuroendocrine tumors, acinar carcinomas, pancreatoblastomas, colloid carcinomas, and solid-pseudopapillary neoplasms [1,3,4].

Apart from all the types mentioned above, pancreatic ductal adenocarcinoma represents the majority of PCs and the term is frequently used synonymous with PC (hence, pancreatic ductal adenocarcinoma will be termed as PC throughout the review). This review discusses the involvement of transcription factors (TFs) of pancreatic developmental pathways in PC.

## Pancreatic ductal adenocarcinoma

### *Epidemiology*

Pancreatic ductal adenocarcinoma, named after its histological origin in the pancreas, is the most common type of pancreatic tumors. It accounts for more than 90% of all diagnosed cases of PC. According to World Cancer Report 2014, PC remained the 12th most

* Corresponding author.
*E-mail address:* mihassan@jmi.ac.in (M.I. Hassan).

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common cancer among the men with 178,000 cases, whereas 11th most frequent cancer in women with estimated 160,000 cases in the year 2012 worldwide. Further, it proved its fatality by killing 330, 000 people worldwide during the same year. This way, it became the seventh most common reason for death worldwide [5]. In the year 2015, an estimated 367,000 new cases of PC were diagnosed worldwide with an estimated 359,000 deaths during the same year [6].

*Genetics of PC*

Like the majority of the cancers and the mechanism of their origin, PC is also initiated in response to mutations in proto-oncogenes, tumor suppressor genes and DNA repair genes. Activating and inactivating mutations in these genes lead to cancer progression. Recent advances in search of a genetic basis for PC have come forward with a number of susceptibility genes that belong to the above-mentioned classes of cancer driver genes. These include mainly K-RAS, BRCA1, BRCA2 (Fanconi anemia DNA repair pathway gene), PLPB2, PTEN and other DNA-repair genes [7]. Germline mutations in these genes contribute to carcinogenesis. Active mutations in a number of oncogenes including KRAS, BRAF, AKT2 etc., play a major role in the onset of PC. Out of these oncogenes, activating mutations of KRAS are the most frequent and are observed in about 95% cases of the PC [8–10]. Inactivation of tumor suppressor genes also leads to tumor growth. Primary development and progression of PC is associated with inactivating mutations in a number of tumor suppressor genes that include TP53, SMAD4, CDKN2A, and STK11 [3,11–13]. Onset and progression of PC is associated with all these genes due to their involvement in various essential developmental and signaling pathways. High levels of autophagy are required for the growth of PC [14]. Alterations in TP53 expression has direct role in autophagy that facilitates PC progression [15,16]. Further, MiT/TFE family of TFs has also been found associated with autophagy assisted growth of PC [17]. Members of MiT/TFE family such as Microphthalmia-associated transcription factor (MiTF), Transcription factor E3 (TFE3), and Transcription factor EB (TFEB) regulate the expression of genes associated of high lysosomal activity that is required of cancer growth [17].

*Risk factors of PC*

Several studies [18–22] have been conducted to find out the relative risk factors of PC apart from genetic alterations. The outcomes of these studies indicate a subsequent role of certain factors such as age, obesity, lifestyle, alcohol or tobacco consumption, and other environmental factors in PC etiology [18]. Age comes out as a determinant factor of PC in a pool of other factors. The majority of PC patients are diagnosed after the 5th decade of the age and above [19]. Similarly, an association of obesity and poor physical habits to the incidence of PC has also been studied. Some dietary factors such as high consumption of saturated fat, processed red meat and low consumption of fruits and vegetables are also associated with risk of PC [19]. Further, smokers have a higher risk of PC in comparison to non-smokers. Consumption of smokeless tobacco products has similar risk amplitude [20]. Studies suggest an association of high alcohol consumption with PC as it may cause severe pancreatitis, which is, in turn, a backing factor of PC [21]. Cancer statistics produced worldwide suggest a higher incidence of PC in developed countries including those of Europe and America in comparison to developing or underdeveloped nations [22]. These data are used to infer the effects of certain environmental factors on carcinogenesis of PC. The lower rates in latterly mentioned nations may be due to underdeveloped diagnosis techniques that may influence that data in various manners. Hence, the association of PC incidence with certain environmental and climatic factors is still a subject of profound debate.

*Precursor lesions of PC*

PC is believed to be developed from a various precursor or preneoplastic lesions that correspond to development and progression of cancer. There are mainly three types of such lesions (Fig. 1) that are studied widely: i) Pancreatic Intraepithelial Neoplasia (PanIN), ii) Intraductal Papillary Neoplasm (IPMN), and iii) Mucinous Cystic Neoplasm (MCN) [23–25]. Although, all these precursor lesions have a tendency to develop into advanced neoplasm, but in the majority of the PCs, PanIN is the key precursor lesion. PanINs are most common and extensively studied lesions that are the representatives of progressive stages of cancer growth. These are characterized as the lesions of small caliber pancreatic ducts. Genetic changes occurring in general class of Adenocarcinomas are frequently observed in PanINs which are classified into three stages based on genetic alteration and morphological makeup and their prevalence: i) PanIN-1 (It is further classified into PanIN-1A and PanIN-1B), ii) PanIN-2 and iii) PanIN-3 [26]. In comparison to PanINs, IPMNs and MCNs are relatively less frequent. MCNs are large cystic lesions that have a characteristic mucin-producing tendency. Both PanINs and IPMNs show substantial similarity at the cellular level, but later on, IPMNs turn into large cystic structures. Studies describing common molecular events among IPMNs and MCNs in comparison to PanINs point towards variations in the approach of these precursor lesions for transforming normal duct cells into malignant ones [1,3,23,25]. Tracing the cellular origin of these precursor lesions and the molecular machinery involved in their development has is in focus of research in recent years [27]. We found evidence of developmental factors such as PDX1, SOX9, HES1, NR5A2 and MIST in origin and progression of these precursor lesions [27–29]. Simultaneous expression of SOX9 with oncogenic KRAS accelerates the formation of precursor lesions [29]. Furthermore, variable expression levels of PDX1 expression of premalignant lesions has also been studied [28].

*Developmental pathways in the origin of PC*

"Genes involved in organ development and differentiation contribute to the ability of tumor cells to proliferate and evade cell death, but they also often alter cell plasticity, i.e. reprogram cell to a state that may give rise to a tumor" [30]. Following notion indicates the importance of developmental genes in carcinogenesis in response to mutations. Donghui et al. [31] in

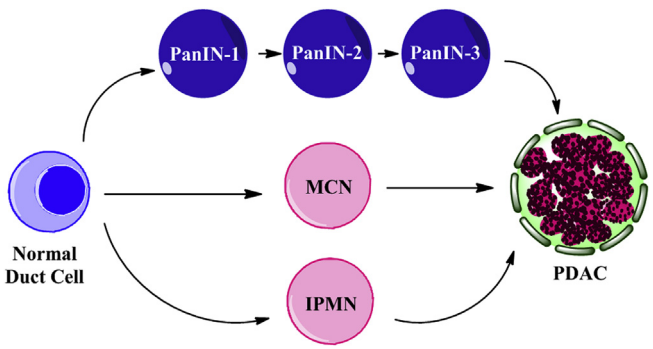


**Fig. 1.** Schematic representation of precursor lesions of pancreatic ductal adenocarcinoma (PDAC). (Abbreviations: PanIN, Pancreatic Intraepithelial Neoplasia; IPMN, Intraductal Papillary Neoplasm; MCN, Mucinous Cystic Neoplasm).

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