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Short report – Lethal and aggressive pancreatic cancer: molecular pathogenesis, cellular heterogeneity, and biomarkers of pancreatic ductal adenocarcinoma

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Abstract. – This short report describes the carcinogenesis of the pancreas leading to pancreatic ductal adenocarcinoma (PDAC) determined by molecular, cellular, and functional heterogeneity. Among the diverse types of pancreatic cancers, PDAC is the most lethal, aggressive, and one of the leading cancers associated with the highest mortality. Pancreatic cellular components like pancreatic stellate cells (PSC), mesenchymal stem cells (MSC), and pancreatic fibroblast cells (PFC) exhibit these properties in PDAC. After the appearance of point mutations in KRAS, the mutations in tumor suppressor genes appear sequentially in the order of CDKN2A, TP53, and SMAD4 that eventually resulting in PDAC development. As of today, there are no effective therapeutic options or treatments available for PDAC. The main difficulty in managing PDAC cases is its defiance to chemotherapy and radiotherapy. There were several attempts to identify a suitable biomarker for the early diagnosis and prognosis of PDAC. Anyway, these recently discovered biomarkers vary in their sensitivity and specificities. Some of the other important and reliable biomarkers for PDAC are carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), cell migration-inducing hyaluronan binding protein (CEMIP), serum fatty acid metabolite PC-594, and micro-RNAs (miRNAs).

Key Words:

Pancreatic ductal adenocarcinoma, Pancreatic cancer, Molecular pathogenesis, Biomarker, Cellular heterogeneity.

Introduction

There are various types of pancreatic cancers with different etiologies. Among pancreatic cancers, PDAC is considered a leading killer disease. PDAC is considered to be one of the devastating cancers prevalent both in developed and developing countries[1]. Due to the anatomical position of the pancreas situated deep inside the abdomen and within the gastrointestinal tract (GIT), any abnormal changes in the pancreas leading to PDAC are often going unnoticed. The lack of PDAC screening tests at the early stage of cancer poses a big issue in the treatment and management. Another problem is a significant number of patients do not develop any overt signs and symptoms at the initial stages of the malignancy. Many researchers have documented that PDAC is one of the notorious, lethal, and aggressive forms of malignancy mankind ever faced[2]. Several oncologists noticed that PDAC exhibited less response to treatment options. Researchers also observed that PDAC is the highly prevalent pancreatic malignancy, and it is formed in the exocrine part of the pancreas[3]. PDAC accounts for a 7.0% overall five-year survival rate. In addition to this, several oncologists noticed that after the diagnosis of PDAC, the survival time is approximately six months.

This short repot focuses on the recent trends in molecular pathogenesis, cellular heterogeneity, and diagnostic prognostic biomarkers of PDAC.

Molecular Pathogenesis

Several research studies in the past two decades on pancreatic cancer have revealed the various process that leads to the development of this cancer. Pancreatic ductal adenocarcinoma is chiefly caused by genetic alterations, such as mutations in oncogenic KRAS and inactivation of tumor suppressor genes CDKN2A, TP53, and SMAD4[4]. These genes regulate various cellular processes

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such as cell proliferation, differentiation, survival, and migration. The KRAS protein cycles through two different conformational states, GTP bound "on" state and GDP bound "off" state. The point mutations in KRAS result in a single amino acid substitution of G12, G13, or Q6121 codons of the GTPase catalytic domain. These point mutations cause conformational block preventing the interaction between KRAS and GTPase activating proteins or preventing GTP hydrolysis[5]. The mutations in KRAS are observed in approximately 92% of the PDAC cases. However, the subsequent inactivation of tumor suppressor genes CDKN2A, TP53, and SMAD4 are required to promote the progression of PDAC[6]. Tumor suppressor genes play an important role to prevent tumorigenesis. After the appearance of KRAS mutation, sequentially, the mutations appear in the order of CDKN2A, TP53, and SMAD4 resulting in PDAC development[6]. CDKN2A encodes the p16/INK4A protein a cyclin-dependent kinase inhibitor responsible for cell cycle senescence. Following the KRAS mutation, the CDKN2A loss is essential for PDAC progression since the p16 might induce senescence sensing the KRAS mutation. Inactivation of p53 is typically observed in advanced PanINs[7].

TP53 is an important tumor suppressor gene that plays a role in PDAC. It encodes the transcription factor p53, which in response to cellular stress or DNA damage promotes cell cycle arrest or apoptosis (Figure 1). Missense mutations of the TP53 cause the ability of P53 to lose its transcription factor function. Following the loss of CDKN2A inactivation of p53 occurs that is typically observed in advanced Pancreatic Intraepithelial Neoplasia (PanINs)[7]. TP53 mutations in PDAC contribute to metastasis (Mutant p53 drives metastasis and overcomes growth arrest/senescence in pancreatic cancer[8]. Other than the TSG, genes such as BRCA1, BRCA2, hMLH1, and hMSH2 are found to lose their function in PDAC[6]. The transforming growth factor-β (TGF-β) has anti-proliferative effects. However, the TGF-β signaling should be transduced by the SMAD4/DCP4, a transcriptional coactivator. Loss of heterozygosity is observed in the majority of the PDAC and is associated with a poorer prognosis[9,10]. The erosion of the telomere has been observed to contribute to PDAC pathogenesis[11].

Cellular Heterogeneity

The pancreas naturally consists of functionally important and morphologically different types of cells. These cells are pancreatic stellate cells (PSC), mesenchymal stem cells (MSC), and pancreatic fibroblast cells (PFC) that are inherently pluripotent in nature. Out of these cells, PSC naturally exhibits high-grade pluripotency. To some extent, MSCs also express this property. PFC originates from PSC and its main function is fat storage for the pancreas. PFCs also originate from other sources like MSC, monocytes, adipocytes, endothelial cells. etc., Naturally, PFCs are silent, dormant with minimal cellular activity, and can transform into cancer-associated fibroblasts (CAF)[12].

Diagnostic and Prognostic Biomarkers

Numerous biomarkers for PDAC are identified and categorized into prognostic, predictive, and diagnostic markers. In PDAC, the poor prognosis is generally due to its aggressive progression, resistance to radiotherapy, chemotherapy, and de-

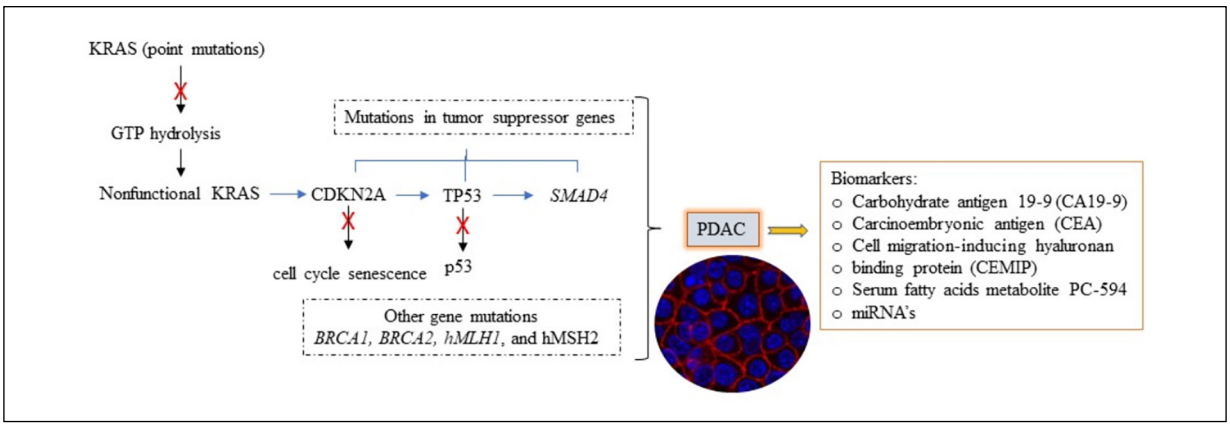

Figure 1. Molecular pathogenesis and biomarkers of PDAC.

layed detection. There is a need for a set of sensitive and accurate biomarkers for the diagnosis and prognosis of PDAC. Carbohydrate antigen 19-9 (CA 19-9) is a very promising candidate as a PDAC biomarker (Figure 1). Other important biomarkers are carcinoembryonic antigen (CEA), cell migration-inducing hyaluronan binding protein (CEMIP), serum fatty acid metabolite PC-594, serum C4b-binding protein α-chain (C4BPA), and micro-RNAs (miRNAs)[13].

Conclusions

PDAC is very aggressive, lethal and one of the leading causes of cancer mortality around the world. It exhibits resistance to chemotherapy and radiotherapy. Early diagnosis is very crucial to increase the life span of PDAC patients. Cellular and functional heterogeneity, rapid oncogenesis, and enhanced molecular pathogenesis are observed in PDAC. Many biomarkers are discovered and can be used for the diagnosis and prognosis of PDAC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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