Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, Bahauddin Zakariya University Multan, Pakistan
ISSN: 2410-6275 June, 2016 Vol: 02 Issue: 02: PP 148-152

Review Article

Pancreatic cancer: From Molecular Biology to Management

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Received: Feb 11, 2016
Revised: June 2, 2016
Accepted: June 7, 2016
Online: June 15, 2016

ABSTRACT

Pancreatic cancer is a lethal disease due to which its early prognosis is necessary. Pancreatic cancer causes the death of many patients. We have to take some preventive measures for our safety. As to quit smoking which is the main cause of PaC. The treatments which are available as surgery, chemotherapy, radiotherapy are not that successful. Due to which we have to know about the genomics of PaC. Which genes are involved in cancer. Genes which altered during PaC are DPC4, p53, and p16 and CDKN2 (Cyclin-Dependent Kinase Inhibitor 2A). though the understanding about those genes we can trace out the actual problem and that problem can be cured. We can treat this disease if we have knowledge about biomarkers which act as a drug target to treat the disease. The available biomarkers now days are miRNAs, CA 19-9 and carcinoembryonic antigen (CEA) which give the early prognosis of cancer possible. Several drug target are discovered that will help out in disease treatment. If we inhibit these inhibitor farnesyltransferase, EGFR tyrosine kinases (epidermal growth factor receptor) ,ERK1/2 (Extracellular Signal-Regulated Kinase) the growth of tumor can be reduced.

Keywords: Smoking; CDKN2; CA19-9 and CAE biomarkers; EGFR tyrosine kinases

91INTRODUCTION:

Pancreatic cancer is a kind of disease in which malignant (cancerous) cells form in the tissues of the pancreas. The pancreas is a gland and located behind the stomach and in front of the spine. The pancreas produces digestive juices and hormones that regulate blood sugar. Pancreatic ductal adenocarcinoma (PDAC) is the main cause of mortality (Jemal et al., 2009)and prognosis of it is very poor, and the ratio of survival of 5-8 months and of 5 years is seen less than 5% regarding all its stages.(Samad et al., 2007) The only cure of the disease is to remove the tumor with surgery. This strategy is only cured 10-20% of the patients (Bilimoria et al., 2007). Most of the patients have the cancer of metastasis stage and they are cured through chemotherapy (Wente et al., 2007). At the time of diagnosis the disease is locally advanced in approximately 30-40% of patients. Neoadjuvant therapies are mainly proposed to that patient for better control of tumor. (Michalski et al., 2007).Neoadjuvant therapy is done to transfer a non resectable tumors to resectable and to increase the rate of resection. There is many proposed treatment for pancreatic cancer if we know the genomics of the patients. As pancreatic cancer is a lethal disease if we detect it in early forms that is very useful. Its early detection can be done if we have exact knowledge about biomarkers that can be used as a tool to detect that type of cancer.

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Stages of pancreatic cancer

There are four stages of pancreatic cancer which are made on the basis of tumor size and its metastasis.

These stages are:

- Stage 1
- Stage 2
- Stage 3
- Stage 4

Stage 1

This stage is further divided into two stages

- Stage 1A
- Stage 1B

In stage 1A the size of the tumor is less than 2cm and it is not spread towards lymph nodes and present only inside the pancreas.

In Stage 1B there is only difference in tumor size. The size of the tumor in this stage is more than 2cm.

Stage 2

This is further divided into two stages

- Stage 2A
- Stage 2B

In stage 2A cancer spread out from pancreas such as in duodenum. But not spread towards the lymph nodes.

In stage 2B the tumor is spread in the lymph nodes but not in the large blood vessels.

Stage 3

This is the advance stage of cancer. In this stage cancer is spread outside the pancreas into the lymph nodes as well as in blood vessels

Stage 4

This is the lethal stage of cancer. In this stage cancer spread into the other body parts as into the lungs etc.

Gene responsible for pancreatic cancer

1. Oncogene
2. Tumor suppressor genes

1) Oncogenes

There are different kind of oncogenes which are responsible for pancreatic cancer as

1.1 Family of ras genes

1.2 Overexpression of p21

1.1 Family of ras genes

Cancer occurs due to some changes in genes. There is gene family named ras genes which in involved in tumor formation. This family consists of three function genes named as H-ras, K-ras and N-ras. an Under normal condition Ras protein in involved in the activation of different effectors as Raf-1, Rac, Rho which are involved in cell proliferation (Adjei, 2001). The mutation occur in the K-ras is point mutation mainly occur on codon 12,13 and 60 which result in alteration of its function and results in tumor formation. Pancreatic cancer occur due to mutation in K-ras gene which result due to point mutation on codon 12 (Almoguera et al., 1988).

1.2 Over expression of p21

Over expression of the p21 protein results in tumor formation. Other suppressor genes which are involved in pancreatic cancer control the regulation of that protein (Biankin et al., 2001). The overexpression of p21 is the early event in cancer formation. The suppressor genes which result in overexpression of this protein are mutated K-ras gene and HER-2/neu genes.

2) Tumor suppressor gene

Tumor suppressor genes catalyze the proteins which protect the cell from carcinoma. The inactivation of these genes results in the formation of tumor.

2.1) Mutation in DPC4/SMAD4 gene

2.2) Mutation in cdkn2 (p16)

2.3) Mutation in p53 gene

2.4) Overexpression of Mdm-2 gene product

2.1) Mutation in DPC4/SMAD4 gene

DPC4/SMAD4 is a tumor suppressor gene. This gene code for a protein which is involved in signal transduction processes with the help of TGF-β superfamily (Hahn et al., 1996). TGF-β is a growth factor which is involved in cell differentiation, wound healing, and proliferation of

cell and in angiogenesis. In normal condition the growth factor does the proliferation and apoptosis of cell and did not allow the cell to cross G1 phase. Any alteration in the signaling pathway results in the abolishment of tumor suppressor function of SMAD4. Due to which tumors start to proliferate without any control. Pancreatic cancer is mainly due to mutation in some genes which are involved in SMAD4 signaling (Grady et al., 1999). Tascilar studied the tumor suppressor action of SMAD4 (Tascilar et al., 2001).

2.2) p16

p16 gene control two suppressor genes. Any alteration in that gene results in tumor formation. p16 is also called cdkn2 (cyclin dependent kinase-2) as it is a cyclin dependent kinase 4 inhibitor. In case of loss of p16 (sdkn2), the amount of cyclin dependent kinase 4 increase which result in Rb protein hyperphosphorylation which ultimately lead to uncontrolled cell proliferation (Caldas et al., 1994).

There are different mechanisms that are involved in inactivation of p16 as:

- Small mutation in p16 gene
- Loss of both the alleles
- Hyper methylation of the gene which results in gene silencing (Merlo et al., 1995)

2.3) p53

Most of the cancer results due to mutation in p53 gene. Mutation in this gene is due to:

- Loss of hetrozygosity
- Alteration in sequence (transition) (Hahn et al., 1995)

p53 gene is involved in transcription of gene expressions and control cell proliferation. Alteration in this gene results in tumor formation.

Name	Character	Role change
K-ras	Gene	Inactive due to mutation
p21	Gene	overexpress
SMAD4	Gene	Disturb due to mutation
p16	Gene	Disturb due to gene mutation
p53	Gene	Disturb due to mutation

2.4) Mdm-2

Mdm-2 gene encodes for a protein whose overexpression results in tumor formation in pancreas (de Oca Luna et al., 1995).

Diagnosis

Early Diagnosis of pancreatic cancer can be done by using biomarkers there are two biomarkers which are being used for the diagnosis of pancreatic cancer but they have low prognosis ability. These are:

- (miRNA)
- carcinoembryonic antigen (CEA)

Using miRNAs we can distinguish between different forms of pancreatic cancer from chronic pancreatitis (CP) patients.

Screening of patients

A dormancy dated of about 10 years between the start of pancreatic cancer and symptoms of the disease has been shown. Thus, there is a benefit of screening; however, there is no agreement as to its best modality, intermission or period. Observational studies of screening include the patients who are at high risk and have used a combination of endoscopic ultrasound, computed tomography imaging, magnetic resonance imaging or endoscopic retrograde cholangio pancreatography (Canto et al., 2006).People having a family history of pancreatic cancer are advised to have genetic counseling and let themselves proper checked. Most investigational protocols begin screening 10 years earlier than the age at which the youngest relative with pancreatic cancer received the diagnosis or at the age of 40–45 years, whichever occurs first.

Risk factors associated with pancreatic cancer

There are several risk factor associated with PaC that include Smoking, diabetes mellitus and pancreatitis. Nicotine which is present in cigarette results in the release of the physiological agonists for β-ARs, the catecholamine stress hormones epinephrine and norepinephrine, from the adrenal medulla (Li and Forsberg, 1996). Elevated level of catecholamine in smokers leads to the development of pancreatic cancer.

Treatment

As in pancreatic cancer several genes are over expressed if we control the expression of those genes we can cure the disease. If we inhibit farnesyltransferase, EGFR tyrosine kinases, , ERK1/2 the growth of tumor can be reduced (in vitro).

Inhibition of COX-2 (Cyclooxygenase 2) have resulted in impressive antitumorigenic effects in vitro (Mimeault et al., 2005). Suppression of vascular endothelial cell growth factor (VEGF) has also shown responses in vitro and in an orthotopic mouse model of PDAC (Fukasawa and Korc, 2004). However, clinical trials with inhibitors of tyrosine kinases, ra, COX-2, VEGF, or the combination of such agents have had not given good results (El-Rayes et al., 2005).

GABABR used as a target to prevent as well as for the therapy of pancreatic cancer. By activating Gaii this receptor can inhibit adenylyl cyclase. This receptor act as a powerful tool for cAMP-dependent signaling, which include the transactivated EGFR-mediated ERK1/2 cascade, that enterprise the propagation and immigration of PDAC. Different from the other therapies that are limited to block individual componetns of signaling network, GABABR counterbalance the whole cAMP-driven stimulatory signaling network which are activated by cell surface receptors coupled with stimulatory G-protein Gαs (Schuller, 2002). Among the families which have Gαs-coupled receptors which are counterbalanced by the GABABR receptor, β-ARs play an important role in pancreatic carcinogenesis. β-ARs act as important intermediaries of growth of cancer as well as invasiveness in carcinoma of lungs, prostrate, colon, stomach, breast and ovary. Moreover GABA and baclofen inhibit β-AR-mediated migration of breast cancer cells and colon cancer cells. Due to which the GABABR may be a used as a promising target for the prevention and treatment of all of types of cancer.

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