

Pharmacogenetics and Personalized Medicine in Pancreatic Cancer

Ali Hosseini Bereshneh¹, Fatemeh Morshedi², Mahsa Hematyar³, Arastoo Kaki¹, and Masoud Garshasbi¹

¹Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran

²Department of Genetics, School of Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran

³Department of Biology, School of Biological Sciences, Kharazmi University, Tehran, Iran

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Abstract- Pancreatic cancer (PC) is a progressive, fatal disease with a high degree of malignancy. More than 40000 people die from this cancer annually in the United States. As a multifactorial condition, PC has a complex nature, and there are several genes and signaling pathways implicated in PC pathogenesis and progression. There are different mutations in master genes including tumor suppressors and oncogenes that lead to Pancreatic intraepithelial neoplasia (PanIN) which is the most common non-invasive precursor lesion of pancreatic cancer. These mutations influence directly or indirectly the cycle of Pharmacodynamics profile. Interactions between genetics and drug metabolism could be considered as one of the most important insights in the personalized medicine and targeted therapy based on the genetic profile of each affected person. In this literature, we will discuss pathogenesis and susceptibility to PC, pharmacogenetics and personalized medicine in pancreatic cancer and scrutinized the most important genes, variations and signaling pathways that influence individualized therapy of PC.

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Introduction

Pancreatic cancer (PC) is a progressive, fatal disease with a high degree of malignancy. Many aspects of the disease are still unknown. According to cancer statistics of United States, the mortality rate of PC in men and women are about 21000 and 20000 cases respectively. Although mortality rate in both sexes is almost similar and is about 7%, but the incidence of PC in women are more than men (1). Our understanding of the genetics and molecular basis of PC has increased dramatically over the past decades and identified several germlines and somatic mutations which could be considered as master genes in the pathogenesis and progression of PC. These mutations could impact directly or indirectly on the cycle pharmacokinetic profile, and they could influence the diagnosis and therapeutic management process of the patients. New approaches such as whole exome next generation sequencing and bioinformatics analysis have yielded to vast, valuable information about the molecular biology of cancers and have discovered numbers of genes and mutations related to cancers as well as new variants which they can be important in cancer diagnosis and prognosis (2). Recently, Whole

Genome Sequencing has detected an average of 63 mutations in both males and females affected. This finding demonstrates PC as a heterogeneous disease (3).

The time and frequency of acquired somatic mutations specifies the duration of the normal tissue conversion into a pancreatic carcinoma tissue. This has been determined through the study of pancreatic epithelial neoplasia and PC non-progressive precursor Lesion (PanIN) (4). PanIN is graded into forms 1 to 3, and these various forms are cytologically and pathologically different. A genetic alteration in PanIN-3 is higher than other types. This higher molecular change in PanIN-3 has shown more susceptibility to progression toward malignancy. Generally, most of the patients have mutations in at least one of the following four known genes (KRAS, CDKN2A, DPC4, P53) (5).

KRAS activating mutations are one of the first genetic events in PC which is mutated in 35% of PanIN-1 and 75% of PanIN-3 lesions (6). Decreasing expression of P16/INK4A, a Tumor Suppressor Gene (T.S.G), similar to upregulation of KRAS, have been shown to influence on the transformation of PC to PanINat early stages and includes around 85-95% of sporadic pancreas cancers. The main reason for this

Corresponding Author: M. Garshasbi

Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran
Tel: +98 21 82884569, Fax: +98 21 82884555, E-mail address: masoud.garshasbi@modares.ac.ir

decline in expression is due to the loss of function of the gene (7). Another factor is the inactivation of (Smad/DPC4) that unlike the previous two factors, occur in the final stages of occurring PC. This protein plays a role in cell development and will be controlled by the TGF-B (8).

One of the most important genes involved in numerous types of malignancies is *P53*, which plays an extensive role in cell cycle regulation. The decrease in expression of *P53* in the PC has been detected in around 50-75 percent of the cases, showing the importance of this gene and its relation to PC (9).

Whole exome Sequencings have been performed on primary tumors and metastatic pancreatic patients and have shown that they have different genetic alterations and they can be divided into distinctive cell colonies according to genetic changes. Metastatic type same as primary tumors has shown heterogeneity, although rate and variety of mutations in both types are different. Analysis of data from sequencing has determined that more than 10 years is needed to develop a primary tumor, and metastasis to form a subclone needs around 6-5 years of extra time (10).

About 7-10% of PC and pre-cancerous syndromes are associated with cancer susceptibility syndromes. In a person diagnosed with pancreatic cancer, several genetic conditions are known, but in up to 70% of patients with a positive family history, no certain specific genetic abnormalities can be found (11).

Peutz-Jeghers syndrome is an inherited disease with Autosomal Dominant (AD) pattern. In 80% of cases, the disease is due to germline mutations in the *STK11/LLD1* genes, along with numerous cancers of the lung, breast, gastrointestinal and sexual tract. These patients are 132 times more at risk of PC than other people (12).

Inflammation of the pancreas is a rare inherited condition. This disease results from defects in 2 trypsinogen genes with the AD pattern, and *SPINK1* gene with the Autosomal Recessive (AR) pattern. It puts the individual 53 times more at risk of the PC in comparison with normal individuals. Approximately 30 to 40 percent of patients affected with this condition will develop progressive PC by the age of 70 (13).

HNPCC is an inherited disease with AD pattern. The disease is caused by germline mutations in protein-coding genes responsible for DNA repairs, such as *MSH1/2*, *MSH6*, and *PMS1/2*. HNPCC leads to an increased risk of colon cancer, endothelial, ovarian, stomach, kidney, and urinary tract as well as pancreatic, but it is very difficult to calculate the risk (14). Melanoma syndrome and multiple family optical moles

have AD genetic pattern, which occurs due to germline mutations in *P16/CDKN2A*. This syndrome leads to a 38 times increase in the risk of PC developing (15).

Conventional treatments for pancreatic cancer

The most important conventional treatments that are used today to treat PC are FOLFIRINOX, Nab-Paclitaxel, Erlotinib. Chemotherapy is done with the help of FOLFIRINOX in metastatic PC or early stages of the disease. FOLFIRINOX is composed of four drugs Oxaliplatin, 5FU, Leucovorin, Irinotecan and in comparison with gemcitabine shows more favorable results. The disadvantage of FOLFIRINOX is severe poisoning. Among the toxications, the 3 and 4 degrees of Neutropenia can be suggested. The tolerance to the drug was not so favorable, the grades 3 or 4 of thrombocytopenia, are associated with grade 3 or 4 of diarrhea and neuropathy-sensory (16,17).

Nab-Paclitaxel (Nanoparticle Albumin Bound) is another chemotherapy drug for PC. A unique feature of the PC is increased stroma which reduces the drug delivery through the primary tumors. So the researchers have tried to strengthen the drug delivery to tumor tissues by targeting the stroma. The result of this research was discovering the Nanoparticle Albumin Bound drug. Fibroblasts surrounding the pancreatic tumors express a large amount of S-propargyl-cysteine (SPRC). This protein has a high binding affinity to the Nab- Paclitaxel (18,19).

Although pancreatic cancer cells show a reduction of expression in SPRC due to hypermethylation of its promoter, it is widely expressed in solid tumors and is involved in several key reactions such as cell invasion, proliferation, and angiogenesis (20).

Despite various constraints between different studies, the comparison between Nab-Paclitaxel with FOLFIRINOX shows that, although the effectiveness of both drugs is the same, but the poisoning and the tolerance to the drug for them are different. Nab-Paclitaxel in combination with gemcitabine, in addition to not causing toxicity, show enough tolerance for patients and therefore can be used as a standard treatment for advanced pancreatic cancer (21).

Target-based therapy or personalized medicine in PC

Personalized Medicine (PM) or Individualized Medicine is a novel approach in the therapy of genetic diseases especially in complex multigenic conditions like cancer which several pathways and genes are involved. In this kind of unique treatment, for example,

two affected individual with the same disease may receive different therapy based on their own origin of genetic profile, mutations, and responses to drugs. So to tackle with the complex conditions like cancer which conventional therapy could not completely be curable or may even not have any useful impact on the inhibition of condition we need PM. To design PM for a therapy panel in cancer we need to know the spectrum of gene mutations, involved signaling pathways and interactions between genetic profile and drugs metabolism (pharmacogenetics). Cancers are heterogeneous in nature, and target-based therapy is one of the best ways to cope with them (22).

Despite the apparent similarities in the PC histologically, to develop into PC, there are different biological pathways involved. Different biological pathways cause different responses to therapeutic interventions. Many attempts to identify the molecular pathways in PC, molecular and genetic changes associated with the biological behavior, the evolution of disease and resistance to treatment have been performed. But Despite these efforts, many of the pathways are still unknown. For this purpose, we need to identify biomarkers and new druggable molecular targets. The activity of different molecules in the signaling pathways is important to show that these biomarkers determine prognosis and prediction of the PC (23). Prognostic markers duty is to show the prognosis of the disease, independent of treatment, based on clinical features or biological conditions of cancer (e.g. pathologic tumor) but in predictive markers, tumors show a response to treatment (24).

In order to benefit more from emerging targeted therapies, we must have the resources, the genetic and molecular classification systems in place of conventional histopathological diagnosis of tumors. This can be done by a better understanding of the molecular changes, identifying potential markers and their relationship with drug response and availability of tools for the measurement of samples (25). HENT1 can be considered as a predictive marker of longevity. Studies on ESPAC1/3 have shown that to increase the expression of the tumor, HENT1 can be a predictive marker of response to gemcitabine. Similar results are shown for RTOG9104, which can increase levels of HENT1 or extend the half-life of gemcitabine (26).

Gemcitabine

Gemcitabine is a nucleoside cytidine analog, which is generally used in the therapy of advanced PC. This hydrophilic molecule is absorbed into the cell with three

nucleoside transporters SLC28A1, SLC28A3, and SLC29A1. Gemcitabine enters the body as a precursor and following a series of biochemical reactions converts to its active form. These reactions are basically phosphorylations, which are carried out by CMPK1, DCK, and nucleoside diphosphate kinase. Finally, the drug is secreted from the body by CDA, NT5C, and DCTD. Gemcitabine has 3 different mechanisms, 1-gemcitabine compete for binding to the DNA and inhibiting DNA synthesis. 2. Prohibits DNA repair by masked termination method. 3-undergoes self-potentialiation (25-27).

In the first mechanism, gemcitabine is converted to phosphorylate Difluorodeoxycytidine by the Deoxycytidine Kinase enzyme. Then Difluorodeoxycytidine-2 phosphate converts to triphosphate. Gemcitabine-2-Phosphate inhibits Ribonucleotide Reductase, the main enzyme involved in the formation of Deoxyribose Cytidimonophosphate. This inhibition lets gemcitabine-3-phosphate to bind to DNA strands during replication. In the second mechanism, gemcitabine allows more than one nucleotide pairing during the replication process. This means that gemcitabine has lower sensitivity to excision repair (by the enzyme exonuclease); hence in this situation, DNA repair is very difficult. The third mechanism, gemcitabine is continuously activated and survived by two mechanisms; the first is reducing the inhibition of Deoxycytidine Kinase and the second mechanism is inhibition of Deoxycytidine Monophosphate Deaminase. This enzyme suppresses by the direct and indirect interaction of gemcitabine-3-Phosphate and gemcitabine-2-Phosphate respectively (27,28).

Pharmacodynamics

Gemcitabine-2-phosphate inhibit Ribonucleotide Reductase enzyme. This enzyme, in turn, causes a biochemical conversion of rNTP to dNTP in the salvage pathway. So gemcitabine reduces dNTP, and finally, cancer cells are depleted of dNTP. Subsequently, DNA replication process blocked. Gemcitabine three phosphorus is the most active form of this drug and can insert into the DNA molecule of cancer cells during replication, causing a nick in the replication fork. This event occurs in the S phase of the cell cycle. As a result, cancer cells which containing damaged DNA, initiate apoptosis process and eventually disappear (29,30).

Pharmacogenomics

Due to the presence of various enzymes involved in drug cycle and also due to polymorphisms in humans,

gemcitabine pharmacogenomics is of high significance.

The main problems of most drugs used for cancer therapy are lack of patients' response as well as severe toxicities resulted from the drug. Although most patients do not show resistance to gemcitabine, several hematologic side effects, especially neutropenia, have been reported. Hence, to discuss gemcitabine pharmacogenomics, we need to mainly focus on carrier gene variants, metabolizing enzymes and other enzymes involved (31,32).

Transporter genes variation

Solute carrier family SLC29

SLC29 also known as *HENT1* is expressed in most cell types. This nucleoside transporter is in the cell membrane and aids nucleoside transfer throughout the membrane. These proteins also react to purines and pyrimidines transfer across the membrane. *SLC29A1* acts as a primary regulator of gemcitabine absorption pathway. Cells that do not express this protein generally show resistance. Encoding gene for this protein is located on 6p21.1. *SLC29A2* has a high tendency towards purines and pyrimidines and is mainly expressed in skeleton muscles. The majority of SNPs related to drug response are observed in *HENT1* gene. The interesting fact is that most polymorphisms are located in the non-coding regions of the gene rather than coding regions. This fact demonstrates the profound effect of the non-coding regions (33,34).

Solute carrier family SLC28

This family is also known as HCNT. *SLC28A1/A2/A3* is members of the nucleoside transporter family. However, *SLC28A1/A3* mainly allows Pyrimidines to go through the cell. *SLC28A1/A2* is primarily expressed in kidney epithelial, intestine and liver and plays a vital role in systematic absorption. Studies have shown that these proteins show differential expressions in various tissues, cells and cancer cells. *SLC28A3* has a high expression in different tissues. The SNPs regarding the encoding gene for this protein are located in coding regions in contrast to *HENT1*. Although genes from the *SLC28A* family have higher polymorphism rate compared to the *SLC29A* family in overall, there has not been any correlations of the SNPs of this gene with drug response or resistance (34,35).

Metabolizing enzymes variants

90 percent of gemcitabine inside the cell is deactivated by cytidinedeaminase (CDA) enzyme. The balance between drug toxicity and drug efficacy is the

most important factor to consider in drug administration. The drug should be only toxic for cancer cells and not toxic for healthy neighboring cells. However, accidental toxicity for neighboring healthy cells is sometimes inevitable. Among all polymorphisms, 3 SNP, have been more reported for affecting drug secretion procedure:

1- rs2072671 (A>C): (Lys27Gly) Allele A lower CDA activity in compared to allele C, therefore, AA genotype will have toxicity and neutropenia.

2- rs1048977 (C>T): (Thr145Thr) amino acid in protein structure has not changed with nucleotide structure. Yet in some cases, differential secretion has been reported in TT comparing CC.

3- rs60369023(G>A) : (Ala70Thr) This SNP is specific to Korean and Japanese. Reduced enzyme activity is observed mainly with allele a (34-36).

Deoxycytidinedeaminase (DCTD)

DCTD with gemcitabine mono-phosphate Deaminates in order to disable it. The inactive form of monophosphate gemcitabine is fluorodeoxyuridinemonophosphate. Despite many studies to investigate the association between the DCTD enzyme variants and gemcitabine metabolism, limited results have been achieved. An example of this association is rs35932500 (T>C), which reduces the DCTD in *in-vitro* conditions. Pharmacokinetic studies has reported an association between the SNPs in the gene for this enzyme formed 3`UTR gemcitabine triphosphate (dFdCTP) (36,37).

CMPK1 cytidine monophosphate kinase1

CMPK1 gene has 7 exons and is located in 1q. The product of this gene, gemcitabine monophosphate is converted into diphosphate. This kind of drug inhibits ribonucleotide reductase. An SNP in the gene encoding this enzyme is rs1044457 (C>T). This SNP is a polymorphism located in 3`UTR. The three phases of the study had different results:

1. dFdCTP formed by a reduction in a variety of patients with non-hematologic tumors.

2. Prolong associated with increased longevity and disease progression in patients with PC.

3. No particular association with treatment response rates in lung cancer patients has been observed.

All three of the above mentioned impact of CC on the SNP has been experimentally confirmed (38,39).

NT5C 5` nucleotidase

Gemcitabine mono-phosphate phosphatase is an enzyme that converts into a state of non-phosphate.

Increased expression of NT5C is similar to increase in resistance to gemcitabine nucleoside analogues. Some studies have shown a positive association between NT5C2 and NT5C3 variations with drug clearance. 3 SNPs (rs3570117, rs6946062, rs11598702) in NT5C2 and 2 SNPs (rs1926029, rs3740384) in NT5C3 are associated with different pharmacokinetic profile in the metabolism of gemcitabine (40,41).

Conclusion

There are several gene networks and signaling pathways which involved in the initiation, progression, and invasion of cancers. Most of the time, these genetic factors interact with each other and also with environmental factors to make the susceptibility to cancers. Pancreatic cancer as one of the most malignant tumors has a complex nature, and several gene mutations and variations linked to this tumor have been recognized up to now. Obviously, irrespective of similar phenotype, the molecular basis of pancreatic cancer could be different. Hence the standard therapy in this condition wouldn't be useful. Conventional therapies which don't consider the genetic profile of the tumor may have different efficacy in different patients and some patients may have an n't suitable response to these therapies. Hence the novel and specific therapies, based on the genetic profile and specific molecular changes are needed. Personalized or individualized medicine could be the favorable solution to cure or inhibit progression of Pancreatic Cancer. The understanding genetic basis of Pancreatic Cancer and well-defined gene profiling would improve individualized medicine.

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