

Role of Genes in the Pathogenesis of Pancreatitis and Pancreatic Cancer

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ABSTRACT

The metastatic progression of pancreatic cancer is greatly attributed to the intercellular communication. It has found serine protease 1 (PRSS1) mutations associated with pancreatic cancer and hereditary pancreatitis. In the long-time "injury-inflammation-cancer" pathway has more and more evidences to support. This review describes the factors closely related to hereditary pancreatitis from the genetic level and how to develop from pancreatitis to pancreatic cancer.

Keywords: pancreatitis; pancreatic cancer; PRSS1; SPINK1; CFTR, CTRC; K-Ras

INTRODUCTION

Pancreatic cancer (PC) is one of the most life-threatening malignancies¹. In 2015, There are about 901,00 new cases of pancreatic cancer and 794,00 deaths in China². The vast majority of pancreatic cancer patients with symptoms and diagnosis are in the terminal stage of cancer³. Only 20% of PC patients can be treated by local excision and the five-year survival rate is 6%^{1,4}. If early diagnostic markers of PC can be discovered, the survival time of patients will be prolonged greatly. With scientific progress, some genes associated with pancreatic cancer have been found, such as trypsin1 protrase (PRSS1), serine protrase inhibitor kazal type 1 (SPINK1), the cystic fibrosis transmembrane conductance regulator (CFTR), the digestive enzyme chymotrypsin C (CTRC) 5-7(<http://pancreasgenetics.org/>). Therefore, it will be great significance to provide a new target for the new mechanism and treatment of pancreatic cancer proliferation and metastasis and early diagnosis of pancreatic cancer, if the association of these genes with pancreatic cancer is clarified. In nineteenth Century, Virchow suggests that there is a link between inflammation and cancer⁸. After there are a lot of studies that Show that chronic inflammation can lead to cancer⁹. So, the chain of inflammation and cancer is deemed to one of nosogenesis of PC.

How Does the Normal Pancreas Develop into Pancreatitis?

PRSS1 gene is described in a continuously updated database which is localized to the T cell receptor beta locus on chromosome 7 (<http://www.genecards.org>) and one of the most common mutated genes of hereditary pancreatitis (HP)¹⁰ and PC⁴. PRSS1 codes trypsinogen, it is a serine protease precursor, secreted by pancreatic acinar cells¹¹. Trypsinogen which has a 7-10-amino acid trypsinogen activation peptide (TAP)¹² is activated into TAP and active trypsin in the duodenum¹². The trypsinogen activated is inhibited by the trypsin inhibitor and degraded by the chymotrypsinogen C in the pancreas. The mutations in the sites of inhibition and degradation can lead to pancreatic autodigestion by triggering activation of the zymogen cascade¹³. L Raphael¹⁴ suggest that there is PRSS1 mutations in 80% patients of hereditary pancreatitis. The amino acid residue 117 (R117H)¹⁵ and 16(A16V)¹⁶ of the PRSS1 gene locus mutations are related to hereditary pancreatitis. Position 117 is the site where trypsin inhibitor cleaves the trypsin, leading to inactivation of trypsin¹². The mutation of R117H prevent trypsin hydrolysis, and pancreatitis occurs^{12,15}. Position 16 is the first amino acid of TAP of the cationic trypsinogen¹⁷. In the PRSS1 gene A16V

mutation, inactive trypsinogen turned into active trypsinogen¹², leading to damage to the pancreas. Meanwhile, accelerated the self activation of trypsin causes chronic inflammation¹⁸

SPINK1, which encodes a trypsin inhibitor, is localized on 5q32 (<http://www.genecards.org>). This protein which is secreted into the pancreatic juice from pancreatic acinar cells⁷ cleaves trypsin at amino acid residue 11715 and hydrolyzes activated trypsin so that trypsin loses activity¹². Trypsin inhibitor inhibits the activity of trypsin as high as 20% in cell¹⁹, and the other 80% of activity is inhibited by alpha-1 antitrypsin coded by AAT. However, the AAT gene has not been reported to be associated with hereditary pancreatitis in Mongolia race. SPINK1 mutation causes that the function of anti-trypsin is changed. And the ability to inhibit trypsin activity decreased or disappeared. The pancreas is in an environment of active trypsin, so it causes injury of the pancreas. Up to now, there are a lot of studies have indicated that the "idiopathic" pancreatitis associates with the SPINK1 gene mutation^{14,19,20,21}, especially the mutation of N34S²⁰.

CFTR is one of the important factors of chronic pancreatitis^{22,23}. Heavy concentrations of HCO₃⁻ which is in succus pancreaticus can inhibit CFTR Cl⁻ channels and the exchange of Cl⁻/HCO₃⁻, in order to prevent the reabsorption of HCO₃⁻ ²⁴ and maintain proper pH in pancreatic duct. But CFTR gene mutation can change the Cl⁻ channel, resulting in the reabsorption of HCO₃⁻ and the decreases of pH in pancreatic duct. As the decreases of pH can accelerate the activation of trypsinogen, the occurrence of pancreatitis is promoted²⁵. The reduction of HCO₃⁻ also leads to the deposition of protein-rich substances, and these protein-rich substances contribute to pancreatic acinar damage and fibrosis²⁶.

CTRC gene encodes Chymotrypsin that can degrade trypsin and trypsinogen ²⁰⁰⁷; Szmola²⁷ et al. have told that CTCR can effectively promote the degradation of trypsinogen and trypsin effectively thereby avoiding pancreas injury by reducing the activation of pancreatic trypsin and trypsinogen²⁸. Sebastian Beer²⁹ et al. have found that CTCR gene mutants are related with pancreatitis. CFTR gene mutants' ability to degrade trypsin is reduced²⁹. It can also enhance the effect of mutation cationic trypsinogen¹⁸. Cationic trypsin mutants with

CTRC gene mutations have higher activity than wild-type cationic trypsinogen¹⁸. These indicate an imbalance in the activation of CTCR-dependent cationic trypsinogen, leading to an increase in trypsin in the pancreas.

How to Develop From CP to PC

In long-term chronic inflammation, cytokines, chemokines, and oxygen free radicals and other media can cause cell and DNA damage. The relationship between the proto-oncogene-Kras and pancreatic cancer has been identified³⁰. Löhrr³¹ showed that the Kras gene is negative in normal humans, and kras gene becomes positive when chronic pancreatitis has been over 3 years. Terumi Kamisawa³² told us that k-ras gene is the most closely related gene to pancreatic cancer.

K-ras protein which is encoded by K-ras gene acts as a "switch"³³. In normal cells, when K-ras protein binds to GDP, in other words, the switch is closed, the downstream signal pathway is not activated. When K-ras protein binds to GTP, the downstream signal pathway can be activated. The "switch" is in balance by Guanine nucleotide exchange factor and GTPase-activating protein³⁴. When the K-ras gene mutates, the binding site of K-ras protein and GTPase-activating protein changes and the GTP can't be hydrolyzed, causing that K-ras protein has been activated and that intracellular signal deranges. Cell continue to multiply or decrease apoptosis by RAF-MEK1/2-ERK1/2 signaling pathway³⁵, leading to normal cells are transformed into cancer cells.

CONCLUSION

Although mutations are found in hereditary pancreatitis and pancreatic cancer, there are still some problems at present: First, the mechanism of pancreatitis and pancreatic cancer has not been elucidated; Second, is a single gene acting or interacting with other genes in PC; Third, only a small part of the susceptibility gene has been identified, and the imbalance between trypsin and antitrypsin cannot be fully explained. Therefore, ongoing studies are necessary to identify the root causes of pancreatic cancer This will help to improve the early diagnosis rate and the survival rate of patients. With the realization of a step by step, we will open a new path away from the pancreatic cancer.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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Role of Genes in the Pathogenesis of Pancreatitis and Pancreatic Cancer

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