Trypsin-antitrypsin Imbalance in Immune Escape and Clonal Proliferation of Pancreatic Cancer

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Abstract

So far it has been failed to confirm whether trypsinogen (PRSS1) besides its homologous genes and TCRVß gene which are co-localized is a gene linkage, though the process of trypsinogen activation has been loaded into textbooks as a classical theory. At present, researchers mainly focus on PRSS1/PRSS2 genes mutations themselves without considering the particularities of genes structures and changes, therefore, cannot explain the immune mechanism of pancreatic cancer. It has been verified that trypsin can serve as a signal factor in stimulating tumor cells proliferation and destroying matrix to promote cell transfer and as a stimulator of lymphocytes to combat with its inhibitor (a1-antitrypsin, a1-AT/AAT), so to play an important role in tumor immune surveillance. Therefore, in order to illuminate the pancreatic cancer immune escape, it is necessary to clarify the correlative spatiotemporal expression of PRSS1/PRSS2/AAT genes. It may provide a theoretical basis for gene treatment of pancreatic cancer to expound the process of trypsinogen gene mutation or abnormal activation leading to AAT gene’s over expression which induced body immune tolerance to cause mutant cells immune escape and clonal proliferation.

Keywords: Trypsinogen; a1 - antitrypsin; Gene co-localization; Micro environment; Pancreatic cancer; Immune escape; Clonal proliferation

Introduction

Various gene mutations are closely associated with pancreatic cancer. K-ras gene mutation is commonly restricted to codon 12 or 13, so it is regarded as a ‘signature’ of pancreatic cancer [1-3]. Thus, Computed tomography (CT)-guided pancreatic puncture is required and it was difficult to carry out in clinical routine because of its costs and the risks of tumor peritoneal or pancrea leakage. Most of the reported results from exon sequencing technology is base of the study of cancer tissue samples, that it is concerned about the variation of the tumor cells themselves; but it was elaborated in this paper is due to the germline mutations caused enzyme expression abnormalities and cause tumors. It has been identified that mutations (p.R122H, p.A121T, p.C139S and p.T137M) or rs10273639 T/T of PRSS1 gene can be found in the exfoliated cells. It is servers as a noninvasive method and offers the more humanistic care to the potential of pancreatic cancer patients [4-9].

Trypsinogen gene (PRSSI1) located in the 7q35 has been proven to be a pathogenic gene of hereditary pancreatitis for nearly 20 years [4-6]. For a long time trypsin has been only used as a tool of biomedical research, while how the balance between trypsin and AAT will influence the cellular microenvironment has rarely been studied. So far it remains unclear that how the co-localization of TCRVß gene with PRSSI1, PRSS2 and their homologous genes [5-7] (Figure 1) affect the maturation and function of lymphocytes. The relationship between trypsin, a1-antitrypsin (AAT) and TCRVß genes’ spatiotemporal expression and tumor besides tumor lymphatic invasion has not been clear [9-11]. Problems such as how PRSSI1 gene mutations affect calcium binding loop or autolysis loop and the auto activation mechanism of trypsinogen being triggered are still

Figure 1: Location Map of Trypsinogen Homologous Genes and TCR Vß Gene [6].

Trypsin gene families T1 ~ T20 are mosaic arrangement with TCR Vß gene family. Of trypsin gene families, only T4, T8 have functions and named PRSSI1 and PRSS2 respectively, and the others are silent in the long river of human evolution.

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Trypsinogen Activation and the Mechanism of Pancreatic Cancer

Trypsinogen genes in mammals and birds constitute a multigene family whose members are found within the beta T cell receptor (TCRβ) locus. In the fully characterized TCRβ loci of human and mouse, clusters of trypsinogen (T) or trypsinogen-like (TL) genes flank a region spanning hundreds of kilobases containing the TCRβ variable gene segments. Analysis of the human TCRβ locus on 7q35 revealed genes coding for the functional trypsinogen proteins PRSS1 and PRSS2, also known, respectively, as the cationic and anionic trypsinogens. The 3.6-kb five-exon genes coding for PRSS1 and PRSS2 are embedded within the first and last units, respectively, of a tandem array of five 10.6-kb duplication units located near the 3' end of the TCRβ locus.

Micro Environmental Destruction and Pancreatic Cancer

The occurrence of pancreatic cancer can be concluded that changes of microenvironment cause gene mutations following with immune tolerance and clonal proliferation, and abnormal activation of trypsinogen leads to less or over activation of other zymogens and destroys the microenvironment of pancreatic cells, together with gene mutations such as k-ras, causing the formation of early tumor cells. Subsequently, trypsin serves as a signal factor in stimulating tumor cells proliferation and destroying matrix to promote cell transfer [13-15] and as a stimulator of lymphocytes to combat with AAT, so to play an important role in mutant cells immune tolerance. This process also conferred cells advantageous selection and made the pancreatic tumor cells become dominant in cell populations. Tumors become more malignant and grow more quickly [16-18] through clonal selection (Figure 2).

New Interpretation of Enzymes and Anti-enzyme Imbalance Causing Tumors

Pancreatic secretory trypsin inhibitor (PSTI) also known as serine protease inhibitor Kazal-type 1 (SPINK1) or tumor-associated trypsin inhibitor (TATI) (Account for 20%) and AAT (Account for about 80%) can antagonize against the activity of trypsin in the physiological state, but over expression of AAT can cause immune tolerance of mutant cells [19-24]. Therefore, it is necessary to analysis the relation between chain expression of PRSS1, PRSS2, AAT besides TCRβ and the occurrence, invasion and clinical outcome of pancreatic cancer. Understanding the effect of space-time chain expression of PRSS1, PRSS2, AAT and TCRβ on transcriptional activation of 7q35 regional genes is an effective ways of clearing the effector genes and cells of abnormal quality and quantity of PRSS1 / PRSS2 enzyme. But, there are no reports on the systemic research of these two relationships.

There are exogenous and endogenous proteases in vivo, such as bacterial toxins and white blood cells disintegration protease, which can damage the microenvironment of liver, pancreas and other organs. But these enzymes can be inhibited by AAT to maintain the integrity of tissue cells. In addition, AAT also can regulate immune response, affect the removal of antigen-antibody immune complex, and activate the complement and inflammatory response [25-29]. AAT can be synthesized by mononuclear cells, alveolar macrophages and epithelial cells and those synthesized by extracellular cells play an important role in the regulation of local tissue injury. Our previous work has demonstrated that trypsin can degrade extracellular matrix and basement membrane to promote the occurrence, invasion and metastasis of pancreatic cancer [15,17,21]. The principle of trypsin induces normal cells turning into cancerous ones is that; trypsin activates cell surface transmembrane receptor PAR-2 which promotes the formation of p-ERK/2 which promotes the formation of p-ERK downstream factor c-fos, then promotes c-fos and c-jun to dimerize into AP-1. Binding to the AP-1 site of PCNA gene, AP-1 regulates the mRNA of PCNA gene on the transcription affected the synthesis of PCNA protein, and then induces carcinogenesis. Corresponding research results were published in Digestive Diseases & Science and Chinese Medical Journal [30,31]. Meanwhile, it also has been confirmed that the theory of AAT compensatory increase is to neutralize and inhibit the activation of trypsin and other proteolytic enzymes so to inhibit the proliferation and spread of tumor cells [23-27]. And another hot issue is that trypsin is a kind of lymphocyte stimulation and its inhibitor-AAT has the function of immune suppression, and the confrontation of them plays an important role in immune surveillance of mutant cells. Recently, our research group also has confirmed that the abnormal activation of trypsinogen led to immune abnormalities. Mutation p.T81M of PRSS1 gene was found in autoimmune pancreatitis family as a pathogenic gene, which causes trypsinogen ectopic activation and results in all trypsin expressed organs injury. So far, this is a relative direct evidence to support that trypsinogen gene mutations are correlated with abnormality of immune system. And the results of the study have been published in World J Gastroenterology [32] (Figure 3).
Trypsin and Pancreatic Cancer

It has been identified that hot mutation spots (p.R122H, p.A121T, p.C139S and p.T137M) of PRSS1 gene were high risk factors of pancreatic cancer, and the clinical outcomes in patients were closely related to the serum level of trypsin [18,20]. Besides, trypsin is a highly specific expression in the tissue of the pancreas (the expression of trypsin in pancreas is 1000 times more than other tissues). Visibly, the abnormal quality and quantity of trypsin caused by trypsinogen gene mutations plays a significant role in the occurrence, invasion and metastasis of pancreatic cancer through trypsin and PAR-2 signal pathway [33-36].

Prospect of Gene Therapy for Pancreatic Cancer

The body's anti-tumor immunity is mainly mediated by activated T lymphocytes, and the confront of trypsin and AAT plays an important role in tumor immunity. Therefore, basing on the relationship between mutations of PRSS1, K-ras besides other genes and the pancreatic cancer, it can lay foundations of early diagnosis and the pancreatic cancer, it can lay foundations of early diagnosis and the pancreatic cancer, it can lay foundations of early diagnosis and

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