

# Pancreatic cancer: from bench to bedside

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**Abstract:** Pancreatic cancer is recognized as the king of carcinoma, and the gap between basic research and clinical practice is difficult to improve the treatment effect. Translational medicine builds an important bridge between pancreatic cancer basic research and clinical practice from the pathogenesis, early diagnosis of pancreatic carcinoma, drug screening, treatment strategies and metastasis prediction. This article will carry on the concrete elaboration to the above several aspects.

**Keywords:** Pancreatic cancer; translational medical research; review

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The incidence of pancreatic cancer is occult, with the rapid progression, the treatment effect and prognosis is very poor, the morbidity and mortality increase with a parallel trend, may be in 2030, ranking second in the malignant tumor mortality rate (1). In 2014 alone, 46 thousand new cases were reported in the United States, and 40 thousand of deaths were reported (2). It is reported (3) that the mortality rate of male pancreatic cancer in China, 2000–2011, was on the rise. Although basic research genome, transcriptome, proteome, metabolome, represented by genomics, molecular biology have developed rapidly, but their results into clinical are lagged behind, huge investment on the basis of research does not make patients better and faster benefit, so the translational medicine came into being, in order to promote the rapid conversion between basic and clinical.

## The concept of translational medicine

Because many clinical problems are not supported by the basic research, and a large number of basic research deviates from clinical practice, it is difficult for clinical application. The concept (4) of translational medicine first proposed by *Lancet*, 1996. Includes the basic research to clinical practice

transformation (bench to bedside, B2B), also the clinical research results into public health promotion strategies (bench to public, B2P) (5). National Institutes of Health (NIH) in 2003 developed a detailed research roadmap of translational medicine, clinical as the center, forming a two-way, open, recursive process research and rapid conversion between basic and clinical, making human health directly, quickly benefit from technological development.

## The translational medicine study of pancreatic cancer

Pancreatic cancer is currently considered a multifactorial disease, multiple genes are involved, multi-step development of the systemic disease, is a complex process of the cancer cell, micro-environment and the body (including genetic, metabolic, immune, etc.) interaction. Although there have been a deeper understanding of the epidemiology of pancreatic cancer, pathogenesis and diagnostic treatment, but the effect of various treatment methods is limited, mainly because of the special nature of the pancreas, the difficulty of early detection and surgical resection, the chemotherapy is less effective. Over the past 30 years, for

the study of molecular mechanisms in pancreatic cancer formation, biological target therapy, the improvement of drug transport in the body and the regulation of the immune system are developing rapidly. However, the study of KRAS has not achieved remarkable results, and restores the suppressor genes such as *TP53* is also difficult to achieve. Targeted therapy efficacy is still unsatisfactory. Treatment of pancreatic cancer in humans is still a great challenge. Translational medicine should be focus on the pathogenesis of pancreatic cancer, early diagnosis, drug screening, treatment strategies and the prediction of recurrence and metastasis.

### *The pathogenesis of pancreatic cancer*

Pancreatic endocrine and exocrine cells both can become cancerous, endocrine cancer are relatively rare, malignant degree is not high, but most exocrine carcinoma has a majority of poor prognosis. Clinically, 90–95% of exocrine pancreatic cancers is the source of the ductal cells, which is commonly referred to as pancreatic cancer. Pancreatic ductal adenocarcinoma (PDAC) has a high degree of malignancy, the mortality rate of patients are diagnosed after one year as high as 95–98%. In recent years, we have produced many new insights in the pathogenesis of pancreatic cancer, Ji found that ERK can promote the degradation of FBW7 by phosphorylation, which affects the function of FBW7 to exert its tumor suppressor function, and promotes the occurrence of pancreatic cancer (6). Bhattacharjee (7) pointed out that cancer can hijack the vitamin D receptor, repair cells damaged by chemotherapy; it is a key way to escape chemotherapy for pancreatic cancer. The researchers also found that the gene-ATDC (ataxia telangiectasia group D complementing gene) takes part in 90% of the growth and proliferation of pancreatic cancer; it plays a key role from the early development of invasive cancer to the metastatic cancer; it reveals the reason why patients with early pancreatic cancer has only a 30% survival rate, that even in the very early stages of invasive cancer, cancer cells have been transferred (8). Gene mutation is the key to the occurrence of cancer, and more than 95% of pancreatic cancer patients have KRAS mutations. Liou found a direct link between KRAS mutations and inflammatory environment (9). The study on the new factor of pancreatic cancer, provides a new basis for the differential diagnosis of pancreatic cancer risk and the development of new therapy, shows that when assessing the risk of pancreatic cancer in individuals, it is necessary to evaluate

the history of the pancreatic cancer and other malignant diseases in the family (10). Many studies have shown that miRNA play a key role in terms of drug resistance. Many directly regulated by the miR-21 target genes. Such as the activation of proto-oncogene *K-ras* gene, *p53*, *p16*, *PDCD4*/*Smad4*, *Bcl-2* and other tumor suppressor gene inactivation are closely related to the incidence of pancreatic cancer, miR-21 in pancreatic cancer cells proved can induce the chemotherapy resistance of gemcitabine (GEM). However, due to the abnormal expression of *miR-21* target genes in cancer, cardiovascular disease, immune system disease, so it is still in the initial stage of pancreatic cancer research, it can't be widely used in clinical. There is a rapid development of the signal pathway in pancreatic cancer. Rac1b's unique signaling pathway makes pancreatic cancer aggressive. Dr. Derek Radisky said: if you can target the intervention Rac1b, may have a significant impact on the treatment of pancreatic cancer (11). Hhat enzymes can be adsorbed onto the surface of fat molecules to facilitate the adsorption of other cells and to transfer information, In cancer, Hedgehog may affect normal cells nearby, guide the secretion of nutrients to supply the cancer cells, and provides the advantage of environment for the growth of cancer cells, and Hedgehog protein in the absence of Hhat enzymes does not play a role. Zhang (12) testified that the use of dovitinib inhibition of the FGFR signal has achieved remarkable antitumor effect, its effect in expressing FGFR specific subtype of FGFR2 IIIb more significantly in patients with pancreatic cancer. Meanwhile Rhim proved to inhibit proliferation of fibrous tissue can't block the growth of pancreatic cancer (13). While Li (14) revealed how the muscle bundle protein helps cancer cells penetrate into the abdominal lining closely packed cells layer, found a potential way to prevent the spread of pancreatic cancer. Ultimately, these research informations can help the doctors better understanding of the pathogenesis of pancreatic cancer.

### *Pancreatic cancer detection means*

Screening and early diagnosis of pancreatic cancer marker is key to achieving secondary prevention. Those proteomic markers, metabolomics markers, microRNAs markers, genetic markers, circulating tumor cells (CTCs) and the emergence of epigenetic markers, provide new ideas for early diagnosis, early intervention, early treatment, early monitoring and evaluation of pancreatic cancer. Researchers from the London cancer research center test blood from 191 patients with pancreatic cancer, identified 14 different

genes, including *BRCA* gene mutation, they can greatly increase the chances of pancreatic cancer, and men may soon be able to predict the risk of pancreatic cancer by genetic testing. In epigenetic, Tjensvoll *et al.* (15) found that early stage pancreatic cancer exist *SLC32A1*, *CSMD2* and *TRH* methylation. Cote (16) expressed through measuring the level of microRNAs molecules circulating in the blood can help determine whether the patient is suffering from pancreatic cancer. The high expression can of miRNA-10b, miRNA-155 and miRNA-106b can be accurately detected in patients with PDAC. Based on these findings, this new detection technique might be used to differentiate between pancreatic cancer and other pancreatitis. The study found *CEACAM1* and *REG3A* did not change significantly in the early pancreatic cancer, and *CA19-9* (>37 U/mL) at the onset of the previous year, with 68% sensitivity, two years before the onset with a sensitivity of 53%, and *CA125* can be combined as an indicator for early diagnosis and prediction of disease prognosis (17). British researchers found that three kinds of protein markers (*LYVE-1*, *REG1A* and *TFF1*) the urine can be found in the early stage of pancreatic cancer, the joint detection makes I-II pancreatic cancer accuracy rate more than 90% (18). Bhasin *et al.* (19) identified an effective and accurate five gene classification method for distinguishing early pancreatic cancer from non-malignant tissues. Because more than 90% of patients with pancreatic cancer are diagnosed at the stage of metastasis, only limited treatment options at this time, so the more early diagnosis is thought to play a major role in prolonging the life expectancy of the patients.

### Research progress of pancreatic cancer targeted therapy

The essence of high infection of pancreatic cancer is the mutation of some key genes (such as *KRAS*, *TP53*, *SMAD4*, etc.). In addition, the surrounding stromal cells and some chemokines also provide a help for the proliferation of tumors. Wu (20) found that *IL-17* cytokine family is an important factor in the regulation of inflammation in the immune response. And use *IL17RB* neutralizing antibodies effectively to inhibit the growth of pancreatic cancer, which provides a new direction for the future treatment. The researchers (21) through the study of the whole genome sequencing and copy number variation (CNV) in 100 patients with PDAC, showed that chromosomal rearrangements in the gene caused widespread damage, which affect key genes, such as *TP53*, *SMAD4*, *CDKN2A*, *ARID1A* and *ROBO2*, and will also

affect some of the new driving factors such as *KDM6A* and *PREX2*. Genetic variation can be used as PDAC biomarkers for characterizing the effect of treatment. The research team (22) using a copy of interleukin-10 (*IL-10*) equipped oncolytic vaccinia virus is expected to be a better treatment of pancreatic cancer, this protein is known to suppress the immune response in mice, but how to suppress *IL-10* anti-viral immunity, enhance anti-tumor immunity remains unclear. Morran (23) indicated that rapamycin can effectively treat pancreatic cancer due to errors caused by *PTEN* gene, in some mice organism, rapamycin may even promote tumor death. *GRP78* protein is able to protect from cancer cell death, but researchers at the University of Minnesota (24) found that the extract of triptolide can inhibit *GRP78*, eventually leading to pancreatic cancer cell death. The activation of ER stress pathway by triptolide suppresses *GRP78*, which provides a novel mechanism to inhibit the growth and survive of pancreatic cancer cell. Martínez-Bosch (25) related pancreatic cancer through inhibit galectin-1, the results showed that the survival rate of mice can lead to an increase of 20%. Andreoli (26) developed a kind of carbon nanotubes, can successfully through the body's defense system to reach the pancreatic cancer cells, and then attack the cancer cells. Hao Jihui, a Chinese scholar led the research group, synthesized a new type of multi-layer phospholipids-mixed polymer nanocarriers, achieving a layered carrying of the three active ingredients (5-Fu, oxaliplatin, irinotecan) in FOLFIRINOX chemotherapy, fill the technology gap of simultaneously carry multiple drug nanocarriers in pancreatic cancer treatment. Bapiro (27) found that GEM is broken by the enzymes in Kennedy Pathway, which may be another principle of GEM worked, joint linoleic acid, can increase the amount of drug in the tumor cells. It is necessary to understand the interaction between GEM and cell metabolism; it will enable us to develop a combination treatment therapy to improve the prognosis of patients with pancreatic cancer.

### The clinical therapy of pancreatic cancer

In 1996, the FDA approved GEM substituted 5-Fu, for the treatment of advanced pancreatic cancer. Although for many years active exploration in the laboratory and clinical, experimented with a variety of cytotoxic drugs, biological therapy and molecular targeted therapy, but the overall efficacy and safety is far from satisfactory, GEM line treatment as the "Gold standard" status of

pancreatic cancer is still difficult to shake. The EU has approved ABRAXANE combined with GEM as first-line therapy for metastatic pancreatic cancer in adult patients. Meanwhile in the United Kingdom a product called plerixafor (AMD3100) drug tested in mice, successfully penetrated the pancreatic cancer cell's outer protective layer, and removal of pancreatic cancer cells in the body in 6 days. And targeting blockage of lysyl oxidase-like protein-2 (LOXL2) monoclonal antibody simtuzumab failed in pancreatic cancer phase II study, compared with placebo, it failed to meet the primary endpoint of the study. Renouf (28) reviewed He reviewed the drug reaction with GEM combined with erlotinib in patients with the mutation of *K-ras* gene. FDA granted necuparanib treatment of pancreatic cancer, which is derived from the unfractionated heparin; it is designed to significantly reduce the anticoagulant activity while preserving antitumor properties related. In herbal medicine (29), India Melia lactone can induce cancer cell death, led to the colony size and number of pancreatic cancer cells decreased by 80%, at the same time, does not damage the normal healthy cells. The researchers Mazur (30) found that a BET family protein inhibitor-JQ1 can inhibit the development of PDAC mice by inhibiting the activity of MYC and inflammatory signals. The histone inhibitor SAHA can amplify the cell death effect with JQ1, and has a more effective inhibition on advanced PDAC. It is not possible to completely remove the cancer tissues from patients with pancreatic cancer in clinical practice. Researchers Martin RC 2nd (31) indicates the irreversible electroporation technology can effectively prolong survival in patients with pancreatic cancer, or may cause some patients to survive extended to seven years, and the side effects caused by much smaller than other operations.

### Expectation

Clinical study needs new ideas, new strategies, new directions and new technologies. Translational medicine brings the new hope to the clinical research. If we can trace the forefront in practice, strengthen independent innovation, will improve the efficacy of treatment. Currently scientists around the world are struggling to study the pathogenesis of pancreatic cancer and constantly looking for new targeted therapies. We believe that in the near future, we can significantly increase the survival rate of patients with pancreatic cancer, improve their quality of life.

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