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Translational Medicine: Are we Ready for the Prime Time?

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Introduction

Translational medicine is an increasingly important field designed to bridge the gap between basic science and clinical care. Academic institutions, industry, and other health organizations commit billions of dollars annually for the development of translational medicine programs and initiatives. In 2006, the National Institutes of Health (NIH) launched the Clinical and Translational Science Award (CTSA) program with the goal of establishing 60 centers of translational research at academic institutes across the country [1]. These efforts are aimed at integrating knowledge gained through basic science research and clinical practice to provide effective and novel strategies for the diagnosis, prevention, and treatment of common diseases.

The human genome project draft sequence, published in 2001, revolutionized the scope and capabilities of translational medicine by enabling researchers to study the entire structure and function of the human genome [2]. This project eventually led to the development of new technologies such as high-throughput techniques and new fields like genomics, proteomics, and metabolomics. Taken together, these advances ushered in a new era of genome-based studies that may elucidate the molecular mechanisms behind diseases such as cancer. In addition, they introduced the possibility of providing personalized medical care that draws upon an individual's genetic information to optimize patient management.

In this article we will focus on Pancreatic Ductal Adenocarcinoma (PDAC) and how genomic information may revolutionize PDAC management. We will discuss how advances in translational medicine may be utilized to accuratelypredict patient survival and design effective and personalized therapies for PDAC patients.

Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC, the fourth leading cause of cancer deaths in the United States, is a highly aggressive disease with a 5-year survival rate below 5% [3]. Early diagnosis of PDAC is difficult owing to a lack of effective biomarkers, vague clinical symptoms, and the highly invasive nature of PDAC tumors. By the time most patients are diagnosed, the disease has advanced to late stage. Surgical resection, the only known curative treatment, is therefore an option for only 10-20% of PDAC patients [4]. Moreover, PDAC is notoriously unresponsive to conventional chemotherapy and radiotherapy.With a mortality rate that nearly equals the incidence rate, it is clear that significant progress needs to be made in both understanding the biology and improving the management of this deadly disease.

Gene Profiling Studies

Gene profiling studies utilizing DNA microarray techniques have helped identify differentially expressed genes in PDAC. In a study by Iacobuzio-Donahue et al. [5] over 400 genes were found to be differentially expressed in PDAC, while ina comparison of gene profiling studies, more than 200 genes were repeatedly identified as being over-expressed in four or more studies [6]. Additionally, Jones et al. [7] found 541 genes to be over-expressed over ten-fold compared to healthy controls. The genes identified by Jones et al. were associated with 12 common molecular pathways including K-Ras, TGF-β,Wnt/notch, integrin and hedgehog signaling. However, the specific genes were found to vary significantly between individuals, reflecting the highly complex nature of this disease [7]. These findings suggest that personalized therapies targeting appropriate deregulated genes in each individual may be critically important for improving the management of PDAC.

The differentiation of PDAC from chronic pancreatitis by gene profiling can be difficult due to similar gene involvement; however, ANXA2 and IGFBP-2 were reported to be expressed at higher levels in PDAC compared to chronic pancreatitis [8]. Gene profiling studies have also been used to identify tumors that are more likely to be responsive to chemotherapy. For example, GSTT1, TOP2A, CASP3 and ABCC2 were found to be differentially expressed in gemcitabine-sensitive PDAC [9].

Genome Wide Association Studies (GWAS)

Genome Wide Association Studies (GWAS) have been used to investigate how Single Nucleotide Polymorphisms (SNPs) are associated with disease traits. Several recent studies have found associations between specific SNPs and increased risk of PDAC. In a PanScan study, SNPs on chromosomes 9q34, 13q22, 1q32, and 5p15 were associated with increased risk for PDAC [10,11]. The 9q34 SNP, found on the first intron of the ABO gene, may explain studies that show people with group O blood type having a higher risk of pancreatic cancer. In a study of the Japanese population, SNPs mapped to chromosomes 6p26, 12p11, and 7I36 were also associated with increased risk for PDAC. In a separate study, SNPs mapped to APC (rs2431238) and NIN (rs10145182) werealso associated with a higher risk of pancreatic cancer [12,13].

GWAS have also been utilized to assess the variable prognosis of PDAC cases. Several studies found a number of SNPs that were associated with differences in overall survival. The mapped SNPs included genes EXO1, RAD54L XRCC1, ATM T-77C, EIF3S10, MGMT, MSH2, MSH3, MSH6, PMS2L3, and TP73 [14,15]. In cases of resectable PDAC, SNPs mapped to genes MDM2 and p27 reflected survival time after treatment, while p73, p16, and MDM2 were associated with faster tumor progression [16]. In addition, the RECQL A159C AA genotype was associated with improved long-term survival in resectable PDAC treated with neoadjuvant gemcitabine, with a frequency of the A allele as 55% in Asian populations, 57% in Caucasian, and 90% in Yoruban populations [17]. Several SNPs have also been associated with drug effectiveness and toxicity. SNPs mapped to CDA c111T, dCK c-1205T,

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dCKA9846G, and hCNT3 A25G were associated with a higher risk of neutropenia toxicity with gemcitabine treatment of resectable PDAC [18]. Li et al. [19] also found that pancreatic cancer cell lines with lower DNA methyltransferase I (DNMT1) expression levels were found to be more sensitive to 5-aza-deoxycytidine (5-Aza-dC) treatment. Future GWAS findings may identify other genetic risk factors for developing PDAC and personalize strategies for PDAC treatment.

Pancreatic Cancer Genetics And Risk

Individuals with a family history of PDAC have a higher risk of being diagnosed with PDAC, suggesting a genetic basis for PDAC incidence. In fact, approximately 5-10% of pancreatic cancer cases are attributable directly to heredity genes. Other known risk factors include tobacco use, obesity, and diabetes. The increased risk may be explained by genetic polymorphisms on genes such as GSTT1 or IGF1 that increase susceptibility to pancreatic cancer in heavy smokers and diabetics, respectively [20]. Mutations in p16, MMR, STK11, and BRCA2 may also suggest a higher risk of developing PDAC. p16 mutations are associated with Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome, which confers a 20 to 34-fold increasedrisk of PDAC [21]. MMR mutations associated with hereditary non-polyposis colon cancer and STK11 mutations associated with Peutz-Jeghers polyposis also correspond to increased risk of PDAC [22]. Similarly, BRCA2 mutations are associated with an increased risk of developing multiple cancer types including pancreatic, breast, ovarian, and prostate cancer [22]. Knowledge of genetic mutations associated with increased susceptibility is vital for the prevention and early detection of disease through genetic screening.

Targeted Therapy

Pancreatic cancer is unresponsive to many common chemotherapy drugs. Gemcitabine, the standard of care, has demonstrated only a modest increase of overall survival of pancreatic cancer patients. The heterogeneity of gene profiles in pancreatic cancer may explain why standard treatment strategies are insufficient to treat many PDAC cases.Through identification of specific differentially expressed genes, molecular targeting approaches may prove to be useful for personalized treatment of this disease.

Ongoing clinical trials have been promising for the use of Epidermal Growth Factor Receptor (EGFR) targeted therapies using small-molecule inhibitors and antibody-based treatments [23]. Other potential therapeutic targets include K-Ras, VEGF, matrix metalloproteinases, SHH, notch and Smad among other targets, although early efforts have not been found to significantly affect clinical outcomes. Pancreatic tumors with mutated BRAF genes may prove to be sensitive to BRAF inhibitors such as vemurafenib, currently approved for use in metastatic melanoma cases [24]. Other chemotherapeutic drugs may be effective in treating small subsets of pancreatic tumors based on the genetic profiles of individual tumors, with a promising outlook on improved clinical outcomes for patients.The attenuation of mutant genes such as K-Ras and Notch through RNA interference has additionally been shown to decrease tumor growth *in vivo*, and may be a promising new therapy [25,26].

Novel therapeutic and diagnostic targets that may be of interest in future studies include the zinc transporter, ZIP4, and pancreatic and duodenal homeobox (PDX-1). ZIP4 was found to be greatly overexpressed in over 50% of examined PDAC samples compared to surrounding benign tissues. Elevated ZIP4 expression was associated with increased intracellular zinc levels, proliferation, and tumor growth [27]. The attenuation of ZIP4 expression byshort hairpin RNA resulted in decreased pancreatic cell proliferation, migration, and invasion as well as increased survival of nude mice with pancreatic cancer xenografts, suggesting that ZIP4 targeted therapies may emerge as a viable approach to pancreatic cancer treatment [28]. Additionally, modulation of PDX-1 expression has been shown to inhibit tumor growth *in vitro* and *in vivo* [29]. Overexpression of PDX-1 has been associated with increased proliferation and invasion, so PDX-1 may serve as a novel diagnostic biomarker and therapeutic target for PDAC.

MicroRNA Expression Profiling

A burgeoning area of interest in genomic profiling for PDAC treatment is the deregulation of microRNAs (miRNAs) in PDAC tumors. MiRNAs are small non-coding RNA molecules that are involved in the post-transcriptional regulation of multiple essential cellular processes such as proliferation, apoptosis, and development [30]. Abnormal expression of miRNAs that target tumor suppressor or oncogenes may be implicated in tumor development and disease progression. MiRNA array and quantitative RT-PCR techniques have identified miRNAs that were commonly over-expressed or down-regulated in pancreatic cancer. In fact, miRNA expression profiling effectively differentiated pancreatic cancer tissue from both normal pancreatic tissue and pancreatitis tissue, suggesting that miRNAs are novel and effective biomarkers for the early diagnosis of PDAC. A number of miRNAs were found to be aberrantly expressed in PDAC, including miR-21, miR-155, miR-221, miR-216, and miR-217, while aberrant expression of miRNAs such as miR-21, miR-10b, and miR-196a were associated with clinical outcomes [31]. In addition to genetic profiles of miRNAs in tissue samples, current studies on miRNAs found in serum samples suggest that the comprehensive diagnosis and prognosis of PDAC may be possible utilizing this technique without the need for more aggressive invasive procedures.

MiRNA-Based Therapies

Both tumor suppressor and oncogenic miRNAs have shown promise as viable therapeutic targets for the treatment of PDAC. Some downstream pathways of tumor suppressor miRNAs include fibroblast growth factor 7 (FGF-7) [32], p53 [33], K-Ras [34], Wnt3a [32], and PDK1/Akt [35]. These pathways may become over-expressed in PDAC tumors due to decreased levels of associated regulatory tumor suppressor miRNAs. When over-expressed, these pathways may promote proliferation, survival, and invasion. To reverse this effect, ectopic expression of tumor suppressor miRNAs, such as miR-96, has been shown to inhibit deregulated target pathways, resulting in decreased proliferation and invasion [34]. This therapy has also been demonstrated *in vivo*. The re-expression of tumor suppressor miRNAs such as let-7, miR-34a, and miR-143/145, which are typically down-regulated in PDAC, resulted in decreased tumor growth in xenograft mouse models [36,37].

Conversely, the silencing of oncogenic miRNAshas also been shown to have therapeutic potential. Oncogenic miRNAs are typically over-expressed in PDAC, thus repressing downstream targets such as E1a-binding protein p300 (EP30) [38], DPC4/Smad4 [39], retinoblastoma protein [40], Spry2 [41], and NF-κB repressing factor [42]. Attenuation of miRNA levels through strategies such as gene knockout and antisense silencing have been shown to inhibit tumor progression as well as improve drug efficacy.

Challenges and Future Work

While current findings in pancreatic cancer research are promising, further work must be done to address several challenges

before effective treatments can be developed. Despite high hopes, novel targeted therapies under development often fail to improve the prognosis of pancreatic cancer cases. The disappointing results may be due to interactions between multiple important signaling pathways and the interactions between the tumor cells and the microenvironment. Overall, a more comprehensive approach targeting multiple signaling pathways and cell types will likely be necessary to overcome the challenge. Olive et al. [43] recently found that drug resistance may also be due to poor vascularization of the PDAC tumor tissue. The stromal tissue that surrounds the tumor promotes poor perfusion of the tumor mass. IPI-926, a hedgehog inhibitor, was shown to increase vascularization and delivery of gemcitabine to the tumor cells; however, further work will be necessary to evaluate the effect in preclinical and clinical trials.Another challenge we face is the ability to effectively deliver therapies. New delivery methods are in various stages of development, but they must be fully established before targeted therapies can be translated into clinical care. Current non-toxic targeted delivery methods include liposomes and nanoparticles, which have been shown to successfully deliver small molecule inhibitors, antibodies, antisense oligonucleotides, and oncolytic viruses in animal models [44]. There is much to come in the future for pancreatic cancer diagnosis and treatment. Personalized genomic information may soon be utilized to develop targeted therapies, accurately diagnose individuals, and improve clinical outcomes.

The development and optimization of new clinical practices will be aided by open access journals such as *Translational Medicine*. The journal, in additional to other journals of the OMICS Publishing Group, will help distribute the most up-to-date findings in pancreatic cancer and other critical scientific topics, and is aimed to translate the new discoveries from bench to bed side. The open access format will accelerate the dissemination of peer-reviewed publications in the international scientific community and hasten the progress of clinically applicable therapies from novel basic science discoveries through the promotion of healthy scientific discourse and collaboration. The OMICS Publishing Group includes over 200 Open Access journals, accessible to all readers, as well as 20,000 editorial members, and a rapid review and publication process to allow current findings to be quickly shared with the scientific community.

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