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Genetic and molecular alterations in pancreatic cancer: Implications for personalized medicine

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Recent advances in human genomics and biotechnologies have profound impacts on medical research and clinical practice. Individual genomic information, including DNA sequences and gene expression profiles, can be used for prediction, prevention, diagnosis, and treatment for many complex diseases. Personalized medicine attempts to tailor medical care to individual patients by incorporating their genomic information. In a case of pancreatic cancer, the fourth leading cause of cancer death in the United States, alteration in many genes as well as molecular profiles in blood, pancreas tissue, and pancreas juice has recently been discovered to be closely associated with tumorigenesis or prognosis of the cancer. This review aims to summarize recent advances of important genes, proteins, and microRNAs that play a critical role in the pathogenesis of pancreatic cancer, and to provide implications for personalized medicine in pancreatic cancer.

Key words: pancreatic cancer • genomics • genetics • biomarker • molecular target • personalized medicine

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Background

The understanding of the genetic basis of disease has progressed tremendously in the last 150 years. The science of genetics began in the 1860s when Gregor Mendel studied inheritance in pea plants (*Pisum sativum*) [1]. In the 1940s, Oswald Avery, Colin MacLeod, and Maclyn McCarty showed DNA was the genetic material [1–3] and later on, in 1953, James Watson and Francis Crick proposed the double-helix model for the structure of DNA [4]. By the 1970's, specific genes for specific proteins had been recognized [5] and some genes had been synthesized in the laboratory [6,7]. There were other major accomplishments in the same time frame: DNA recombination, sequencing, and site-directed mutagenesis technologies were developed [8–13]; the first complete RNA genome of bacteriophage MS2 and the DNA genome of bacteriophage φX174 were sequenced in 1972 and 1977, respectively [14,15]. The 1980's witnessed the development of polymerase chain reaction (PCR) technology by Kary Mullis [16], and in 1995, the genome of *Haemophilus influenzae* was the first bacterial genome sequenced using the whole-genome shotgun sequencing technology [17]. The Human Genome Project (HGP) began in 1990 and was completed in 2003 by the International Human Genome Sequencing Consortium [18–20]. The reference genome produced by the HGP largely came from a single anonymous male donor from Buffalo, New York [21]. After HGP, several important human genome-related projects have been carried out, including the International HapMap Project, which used DNA samples from 270 individuals [22–24], the 1000 Genomes Project [25,26], the Cancer Genome Atlas, the Cancer Genome Anatomy Project, and the Cancer Genome Characterization Initiative (Figure 1). These human genome projects have enormous health applications in regards to the susceptibility, diagnosis, monitoring, prevention, and treatment of diseases. Genomics and genetics are playing an increasingly important role in the practice of medicine in the post-genomic era as the studies show that genomic or genetic variability may affect health, disease, and responses to drugs and environmental factors. An emerging practice of medicine, termed personalized medicine, uses an individual's genomic or genetic profile to guide medical decisions. This review focuses mainly on recent discoveries of important genes, proteins, and microRNAs (miRNAs) that may play a critical role in the pathogenesis of pancreatic cancer, and in the development of new strategies for the prevention and treatment of this deadly disease.

Personalized Medicine

As our understanding of the human genome increases, the Genomic and Personalized Medicine Act was proposed in 2006 [27]. The President's Council on Advisors on Science and Technology has defined Personalized Medicine, referring "to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not". [28]. Typically, a personalized medicine program (PMP) takes place in multidisciplinary clinics where physicians and scientists tailor medical decisions to the individual patient based on the molecular analysis of patient samples. A PMP should establish clinical and bioinformatics databases, and bio-banks for samples, such as blood and tissues. A PMP can also provide significant research opportunities for translating genetic information into clinical practice [29,30] (Figure 2). For example, the U.S. Food and Drug Administration (FDA) has approved more than 50 targeted therapies, including antibody and small-molecule drugs, vaccines, and gene therapies, which can be used for the treatment of specific subsets of cancer types based on the gene expression profile of the cancer [31]. FDA has also approved more than 100 drugs with pharmacogenomic information in their labels, such as specific warnings or actions on dosing and adverse effects based on the patient's genetic or molecular information [32]. Genetic information can also be used to decide whether to perform prophylactic surgeries to prevent certain cancers in high risk populations. For example, prophylactic mastectomy has been performed in women who have a family history of breast cancer or/and carry BRCA1 or BRCA2 mutations, therefore reducing the incidence of breast cancer [33]. Personalized medicine can be applied to patients with pancreatic cancer [34].

In 2013, pancreatic cancer is the 10th most commonly diagnosed cancer and the fourth leading cause of cancer death in the United States [35]; estimates indicate that about 45,220 new cases will be diagnosed and that 38,460 people will die from pancreatic cancer [36,37]. The incidence of pancreatic cancer has been slowly rising over the past 10 years. The one- and five-year survival rates for pancreatic cancer are 27% and 6%, respectively, which are the lowest survival rate of all the major cancers [34–36]. The majority of the patients are diagnosed with pancreatic cancer at the late stage, and are not eligible for surgical resection [37,38]. Recent advances in human genomics or genetics provide new opportunities to understand the impact of genetic and molecular alterations on pancreatic cancer [39–42] as well as provide implications for personalized medicine in this deadly cancer.

Oncogenes in Pancreatic Cancer

Pancreatic cancer is a disease with a wide range of genetic alterations, including germ line and somatic mutations.

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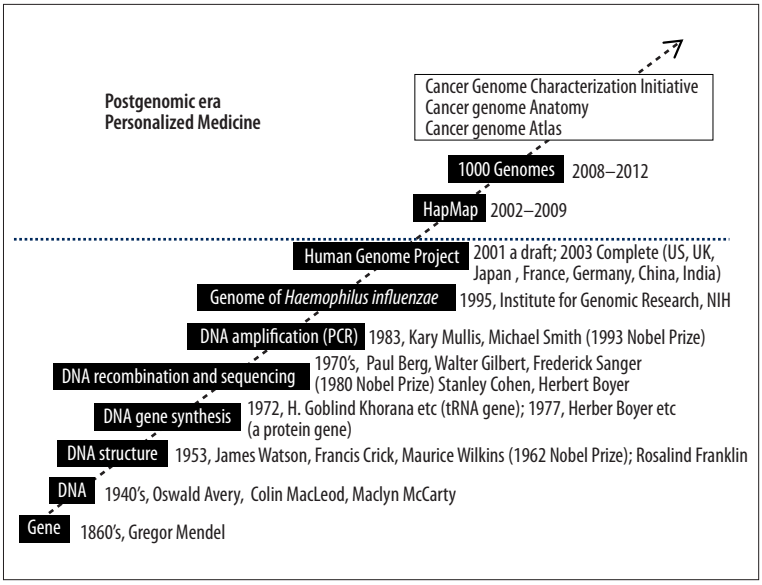

Figure 1. Major milestones of genetic and genomic research. Over past 150 years, discoveries of genetic and genomic research as well as the development of new technologies have enormous impacts on the understanding of the health and disease of human being. The genome era began in 1995 with the publication of the genome of the bacterium Haemophilus influenza [17] and ended in 2001 when human genome was sequenced [18–20]. One of major goals of genomic research in the post-genomic era is to further understand the functional relationship between genomics and human disease, translating genomic information into clinical care tailored to the individual patient, termed personalized medicine.

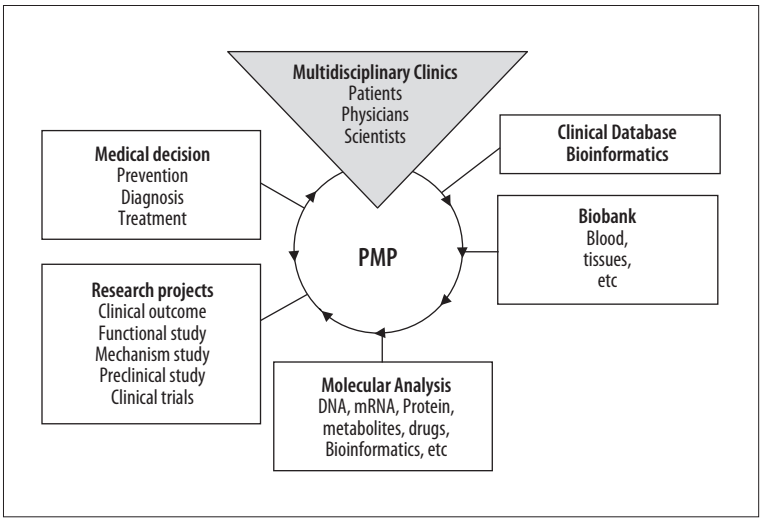

Figure 2. Personalized medicine program (PMP). Personalized medicine is a new health care model in the post-genomic era. Individual genomic and molecular information can be used by physicians and scientists to make medical decisions tailored to individual patients.

For example, a recent whole exome sequencing analysis of 99 pancreatic cancer specimens found 2,016 non-silent mutations and 1,628 copy-number variations [43]. Sixteen significantly mutated genes were discovered, including KRAS, TP53, CDKN2A, SMAD4, MLL3, TGFBR2, ARID1A, SF3B1, EPC1, ARID2, ATM, ZIM2, MAP2K4, NALCN, SLC16A4, and MAGEA6 [43]. Interestingly, this study indicates that somatic aberrations of axon guidance genes may play a critical role in pancreatic carcinogenesis [43]. The most impressive change of an oncogene in pancreatic cancer cells is the mutation of KRAS, which is present in over 90% of pancreatic cancers and in 20% to 30% of all human malignancies [44]. KRAS is closely associated with a series of important cellular functions including cell survival, cell differentiation, and cell proliferation. KRAS is mutated and activated most often on codon 12 and sometimes on codons 61 and 13 [44]. Mutated KRAS has the ability of inducing a ductal precancerous lesion with strong proliferative capacity [39] and the mutation frequently happens in pancreatic duct multifocal hyperplastic foci, a kind of precancerous lesion [45]. An important function of mutated KRAS is to activate several related pathways. The PI3K-AKT pathway, which plays a role in cell survival and cell proliferation, is the best example among these pathways. Genetic mutations could also happen in these pathways. It has been reported that there are four missense mutations in nine exons of PIK3CA in 36 specimens of intraductal papillary mucinous neoplasm or carcinoma [46]. Upregulation of AKT has been observed in approximately 10% of pancreatic carcinomas, thus suggesting that such upregulation may contribute to the malignant phenotype [47]. Furthermore, the activation of AKT in pancreatic cancer is mediated by HER-2/neu over-expression [48] and it has been found that BRAF is mutated in 33% of KRAS-wild-type carcinomas [49]. KRAS activates MEK and ERK1/2, which play important roles in angiogenesis, cell proliferation, cell apoptosis, cancer

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cell migration, and cell cycle regulation [50]. When glypican-1 (GPC1) is present in KRAS mutated mouse models, it can enhance tumor invasion, growth, and angiogenesis of pancreatic cancer, suggesting that GPC-1 is a novel therapeutic target [51].

The Notch pathway, which involved in cell proliferation, cell differentiation and cell apoptosis, plays an important role in pancreatic cancer [52]. It participates in pancreatic tumorigenesis expanding a subpopulation of undifferentiated pancreatic precursor cells through a TGF-α-mediated mechanism [53]. Inhibition of Notch pathway by γ-secretase inhibitor has been explored as a new therapeutic strategy for pancreatic cancer [54]. The Hedgehog pathway also plays a role in the metastasis of pancreatic cancer, and Hedgehog signaling inhibitors can reduce metastasis [55]. The STAT3 transcription factor seems to be involved in cell self-renewal, cell survival, metastasis, and cell apoptosis. STAT3 activation is often present in several precancerous lesions [56]. Silencing the STAT3 gene can induce down-regulation of VEGF and MMP-2, suggesting a key role for STAT3 in angiogenesis of pancreatic cancer [57]. STAT3 inhibitors have potential for the treatment of pancreatic cancer.

Tumor Suppressor Genes in Pancreatic Cancer

Tumor-suppressor genes regulate the cell cycle or cell apoptosis protecting cells from tumorigenesis. Gene p53 controls transcription of p21, a cyclin-dependent kinase inhibitor, mediating G1 block [58–60]; Gene p53 also has a close relationship with G2/M block [61–63] and can upregulate PUMA (p53 upregulated modulator of apoptosis), which binds to Bcl-2, inducing programmed cell death [64]. Seventy-five percent of all pancreatic cancers carry p53 mutations [65], making this gene one of the most mutated tumor suppressor genes in pancreatic cancer. In addition, expression of DPC4 (Deleted in Pancreatic Cancer, locus 4) has been correlated with distant spread metastasis of pancreatic cancer [66,67]. It has been reported that loss of DPC4 expression was closely related to a lower patient survival rate [68]. Mutation of LKB1 (liver kinase B1) gene can cause Peutz-Jeghers syndrome, an autosomal dominant disorder involved in pancreatic cancer. LKB1 participates in cell polarity regulation and in cellular responses to external stresses [69,70]. By mutation and deletion, INK4a (p16), a cyclin-dependent kinase inhibitor, is down-regulated in almost 95% of pancreatic cancers cases. Mutation of INK4a gene has been linked to a rare syndrome called familial atypical mole-malignant melanoma, whose most significant feature is being associated with high incidence of pancreatic cancer [71,72]. Another study detected homozygous deletions of the MKK4 (mitogen-activated protein kinase kinase 4) gene in about 2% of pancreatic cancer cases [73]. MKK4 is believed to participate in a signaling pathway of a tumor suppressing function as a downstream molecule of DPC4, p16, p53, and BRCA2 genes [73].

CNVs and SNPs in Pancreatic Cancer

Besides gene mutations, copy-number variations (CNVs) are often seen in cancer cells. In a study of familial pancreatic cancer (FPC), there were 93 non-redundant CNVs in 50 cases, including 53 losses and 40 gains. FPC-specific CNVs clustered at 88 RefSeq genes' coding regions [74]. A single-nucleotide polymorphism (SNP) is a single nucleotide difference in the genome that can occur in coding and non-coding regions. SNPs can affect humans in regard to their responses to disease, drugs, and vaccines. For example, SNPs rs505922 and rs9543325 are associated with higher risk of pancreatic cancer, and SNPs rs9350 and rs148242 are associated with lower overall survival of both stage 1 and stage II pancreatic cancer [75]. An average of 63 genetic alterations has been shown in each of 24 pancreatic cancer cases studied; most of the genetic changes are point mutations and only some of these gene mutations may produce physiological changes [76].

Molecular Targets in Pancreatic Cancer

As mentioned above, the KRAS mutation is present in more than 90% of pancreatic cancers. The role of KRAS in pancreatic cancer has been further supported by the development of mouse models carrying the KrasG12D mutation, with or without inactivation of tumor suppressor gene p53 [39,40,77,78]. These mouse models have been well characterized and indicate that KrasG12D activates Hedgehog-mediated signaling and inflammatory pathways, and that it is essential for tumor maintenance [78]. Reolysin, an oncolytic virus, replicates in the cells that have an activated KRAS. Reolysin replicates in and eventually kills KRAS-activated tumour cells. Thus, it has shown a therapeutic potential for many solid cancers including pancreatic cancer with KRAS mutation [79].

There are several new drugs being investigated for their possible role inhibiting cancer signaling pathways, including VEGFR and PDGFR inhibitors (sorafenib and sunitinib), MEK1/2 inhibitor (AS703026), and c-Met and VEGFR-2 inhibitor (foretinib). In the PI3k pathway, mTOR is one of the key kinases. Everolimus, an mTOR inhibitor, was reported to inhibit tumor growth in mouse models [80]. The γ-secretase inhibitor MRK003 has shown a tumor inhibitory effect, and the combination of MRK003 with gemcitabine has been reported to prolong survival of mice with pancreatic cancer [81]. A blocker of the aberrant Hedgehog signaling pathway, called IPI-269609, has been shown to inhibit systemic metastases of pancreatic cancer through a possible mechanism of targeting subsets of cancer stem cells in the animal model [82].

Mutations of BRCA2, FANCC, and FANCG genes in pancreatic cancer have been reported to cause hypersensitivity to

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interstrand cross-linkers such as mitomycin C (MMC), cisplatin, chlorambucil, and melphalan [83]. Gene therapy using Rexin-G, a nonreplicative pathology-targeted retroviral vector bearing a cytocidal cyclin G1 construct, was tested in a clinical trial (phase I/II) in a gemcitabine-resistant pancreatic cancer and showed to be well-tolerated and to have an excellent safety [84].

Proteomics of Pancreatic Cancer Tissues

The study of proteomics of pancreatic cancer tissues is currently a very active field of research. There is tremendous interest in the differential protein expression profiles in different organs and body fluids affected by pancreatic cancer in order to search for biomarkers that could be used for early diagnosis, to determine responsiveness to treatment, and to understand the molecular mechanisms of tumor biology. These studies have been done using diverse techniques and the results have revealed a list of proteomic changes associated with pancreatic cancer.

For example, the 2-DE (two-dimensional gel electrophoresis) and MALDI-TOF-MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) analyses of 12 cases of pancreatic cancer showed 111 changes in protein expression levels. Seventy proteins were up-regulated and 41 were down-regulated when compared with their corresponding normal tissues. The overexpression of two of these proteins, fascin and cathepsin, was confirmed in cancer tissues using immunohistochemistry [85]. A separate study identified 30 novel potential biomarkers differentially expressed in pancreatic cancer tissues and one of the potential biomarkers, TBX4 (T-Box 4), was correlated with cancer differentiation [86]. Other molecules were also upregulated: glycolytic proteins (α-enolase, GAPDH, and triosephosphate isomerase) and transgelin were highly expressed in pancreatic cancer tissues [87]; anterior gradient homolog 2, syncollin, olfactomedin-4, polymeric immunoglobulin receptor, and collagen alpha-1(VI) chain proteins were upregulated in pancreatic cancer [88]. Many studies have demonstrated that the S100 protein family is up-regulated in human pancreatic cancer tissue [89]; S100A11 expression is three times higher in pancreatic cancer tissues than in normal pancreatic tissues; and S100A4, S100A6, and S100A10 showed a similar change [90–93]. Some of these differentially expressed proteins, such as biglycan, PEDF (pigment epithelium-derived factor), TSP2 (thrombospondin-2), and TGF-β (transforming growth factor β), have the potential of becoming diagnostic markers [94]. More proteins, including annexin A4, cyclophilin A, cathepsin D, galectin-1, 14-3-3zeta, α-enolase, peroxiredoxin I, TM2, and S100A8, are also potential markers for early diagnosis [95]. Other proteins, such as GRP-78 (glucose-regulated protein 78), MIF (macrophage migration inhibitory factor), and annexin A5, seem to be promising targets for pancreatic cancer therapy [96]. Gelsolin is closely associated with lymph node metastasis [97], and radixin, moesin and c14orf166 could be considered as metastasis-associated protein markers for pancreatic cancer [98]. Overexpression of NEDD9, FOXC1, ECH1, OLFM4, and STML2 is associated with poor prognosis [99–101] and the expression of Nm23/NDPK-A [102], RKIP [103], CX3CL1/CX3CR1 [104], Ack1 tyrosine kinase [105], HMGA1, HMGA2 [106], and FOXM1 [107] has the same clinical significance.

Plasma or Serum Biomarkers for Pancreatic Cancer

Currently, the serum carbohydrate antigen 19-9 (CA19-9) is a clinical biomarker for pancreatic cancer; however it has modest sensitivity and specificity for early detection [108]. There are many other promising biomarkers under investigation. For example, fibrinogen gamma has been identified as a potential tumor marker for pancreatic cancer especially at the hypercoagulable state [109]. It has been reported that the serum levels of sialylated plasma protease C1 inhibitor and the N83 glycosylation of 1-antitrypsin are increased in patients with pancreatic cancer [110], suggesting that they might also be used as disease biomarkers. The plasma levels of apolipoprotein A1, transthyretin, apolipoprotein E, gelsolin, lumican, and tissue inhibitor of metalloproteinase 1 have a close correlation with pancreatic cancer, but not with chronic pancreatitis or biliary duct obstruction [111,112]. The serum levels of several proteins, including heat shock protein 27 (HSP27), HSP70, PGK1, HMGB1, and DJ-1 are associated with pancreatic cancer with high sensitivity and specificity [113–117]. By using MALDI-TOF MS-based serum peptidome profiling analysis, serum platelet factor 4 was found to serve as a valuable biomarker for pancreatic cancer with 86% sensitivity and 98% specificity [118]. The decrease of serum CXCL7 (CXC chemokine ligand 7) levels has been consistently associated with stage I and II pancreatic cancer [119]. According to 2-DE analyses and mass spectroscopic identification, five proteins were successfully associated with pancreatic carcinoma: cyclin I, Rab GDP dissociation inhibitor beta (GDI2), α1 antitrypsin precursor, haptoglobin precursor, and serotransferrin precursor [120]. An increase in serum phosphoprotein ERK1/2 levels was observed in 82% of patients with pancreatic cancer [121]. Using DIGE (difference gel electrophoresis) and LC-MS/MS (liquid chromatography-tandem mass spectrometry) analyses to study plasma samples of 10 patients with pancreatic cancer before and after surgical resection, 16 plasma proteins were found to correlate with tumor burdens (complement component 3, a-1-B glycoprotein, vitamin D binding protein, apolipoprotein A IV, complement component C4A, hemopexin, B-2 microglobulin, amyloid, P component, a-2 macroglobulin, complement

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factor H and pigment epithelial-differentiating factor) [122]. Interestingly, many metabolic enzymes from pancreatic cancer cells induced the production of specific autoantibodies in patients with pancreatic cancer, raising the possibility that they could be used in immunotherapy [123].

Proteins in Pancreatic Juice

Analyzing the protein profile of pancreatic juice is a valuable approach to diagnose pancreatic cancer. A study of using isotope-code affinity tag (ICAT) technology and MS/MS analysis showed a substantial change in the concentration of 30 (24 overexpressed and 6 underexpressed) out of 105 proteins identified in the pancreatic juice obtained from pancreatic cancer patients compared with controls; and the differential overexpression of IGFBP2 (insulin-like growth factor binding protein-2) was further validated by Western blot analysis [124]. Another study showed that there are 14 proteins up-regulated, including MMP-9, DJ-1 and A1BG, and 10 proteins down-regulated in cancerous pancreatic juice [125]. Other studies showed increased levels of REG1α (regenerating islet derived protein 1 alpha) [126] and PAP-2 (pancreatitis-associated protein-2) [127], and decreased levels of lithostathine Ia [128] in the pancreatic juice of pancreatic cancer patients. Furthermore, protein analysis of the fluid from cystic pancreatic lesions revealed a concentration of carcinoembryonic antigen (CEA) that was higher than the CEA concentration in control samples [129]. Finally, the combination of RCAS1 (receptor-binding cancer-associated surface antigen) and CEA measurements and cytology in pancreatic juice could be another effective method for detecting pancreatic cancer [130].

MiRNAs in Pancreatic Cancer

miRNA is a class of non-coding single-stranded, 18 to 24 nucleotides long RNA molecules that is present in eukaryotic cells and can regulate their target genes at mRNA levels [131–135]. In 1993, Rosalind Lee, Rhonda Feinbaum, and Victor Ambros discovered the first miRNA while studying the role of gene lin-14 in *C. elegans* development [136]. It is estimated that the human genome has over 1000 miRNAs [137], which may target about 60% of protein genes (Figure 3) [138,139]. Many studies have shown that miRNAs play important roles in pancreas tumorigenesis [139,140]; some miRNAs have been reported to have oncogenic functions, while others have tumor suppressor functions. We tested 10 pancreatic cancer cell lines and 17 pairs of pancreatic cancer and normal tissues and found that 8 miRNAs were significantly up-regulated (miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b, miR-15b, and miR-95) [141]. Another study showed that miR-21, miR-155, miR-210, miR-221, and miR-222 were upregulated in ductal pancreatic adenocarcinoma tissues, while miR-31, miR-122, miR-145, and

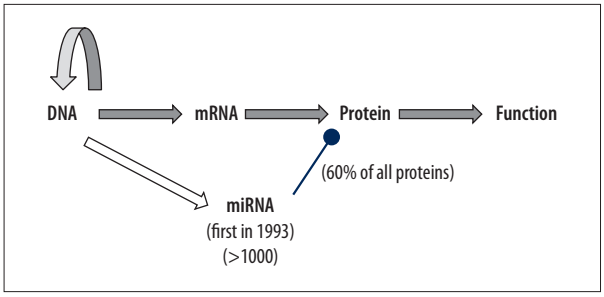

Figure 3. Central dogma of molecular biology. Specific genetic information in DNA (gene) is transcribed into a specific messenger RNA (mRNA), which is translated into a specific protein. miRNA is added into the central dogma to expand the regulation of mRNA translation.

miR-146a were downregulated [142]. In a separate study, 11 miRNAs were strongly up-regulated (hsa-miR-31, -143, -145, -146a, -150, -155, -196a, -196b, -210, -222, and -223), while 11 miRNAs were strongly down-regulated (hsa-miR-29c, -30a-3p, -96, -130b, -141,-148a, -148b, -216, -217, -375, and -494) in pancreatic cancer samples [143]. More studies confirmed differential expression of miRNAs in human pancreatic cancer samples [144,145]. For example, miR-205 was up-regulated more than 600-fold in human pancreatic cancer cell lines, and high levels could also be detected in five out of eight pancreatic cancer tissues [143]. The analysis of pancreatic cancer biopsies revealed that 10 miRNAs were up-regulated (miR-486-5p, miR-451, miR-92a, miR-423-5p, miR-124, miR-3687, miR-1246, miR-1275, miR-17, and miR-320), while 10 miRNAs were down-regulated (miR-4286, let-7f, miR-720, let-7d, miR-1280, miR-200c, miR-26a, let-7c, miR-146a, and let-7b) [146].

It has been reported that several specific upregulated or down-regulated miRNAs in pancreatic cancer contribute to tumor cell growth by targeting to their specific target molecules. For example, oncogenic miR-10a and miR-301a can specifically target HOXA1 and Bim mRNA, respectively [147,148]; while tumor suppressor miR-126, miR-150, miR-34, and miR-148b can specifically target ADAM9, MUC4, Bcl-2/Notch1/2, and AMPKα1, respectively [117,149-151]. A mouse model study showed that Let-7b and miR-495 are required to establish and maintain pancreatic acinar cell differentiation and prevent metaplasia of these cells by repressing HNF6 (hepatocyte nuclear factor-6) gene expression [152].

Increase of circulating miRNAs, including miR-21, miR-25, miR-103, miR-151, miR-210, miR-155 and miR-196, had a close correlation with chemo resistance in patients with pancreatic cancer [153,154]. Furthermore, a specific profile of miRNAs in pleural fluid may be associated with liver metastasis of pancreatic cancer [153].

Understanding the differential expression and functional roles of miRNAs in pancreatic cancer has great potential clinical

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applications. A new panel of 19 miRNAs was used to distinguish pancreatic cancer from normal tissues with 98% sensitivity [144]. Combining the results of circulating miR-16 and miR-196a with CA19-9 was an effective strategy for the diagnosis of pancreatic cancer [155].

Evaluating the down-regulation of miR-217 and the up-regulation of miR-196a could help distinguish between pancreatic cancer and normal pancreas or other chronic diseases of pancreas [141,143]. Another miRNA molecule, miR-211, was identified as a prognostic factor of pancreatic cancer [156] and miR-10b was recognized as a novel diagnostic marker [157]. A new synthetic compound called CDF was reported to inhibit pancreatic cancer cell growth in mouse models through downregulation of miR-21 and upregulation of miR-200 [158]. Antisense oligonucleotides against miR-21 and miR-221 sensitized pancreatic cancer cell lines *in vitro* to the effect of gemcitabine [159].

Other Important Molecules

Epidermal growth factor receptor (EGFR) is a critical molecule for tumorigenesis in many organs. Several EGFR inhibitors, including gefitinib, erlotinib and cetuximab, have been developed for the treatment of different types of cancers. KRAS-induced pancreatic cancer formation requires activation of EGFR [160]. Erlotinib effectively inhibits the proliferation of pancreatic cancer cell lines *in vitro* [161] and in a clinical trial. Erlotinib treatment improved the overall survival of patients with KRAS wild type pancreatic cancer [162]. Increased serum levels of retinol binding protein, NGAL (neutrophil gelatinase-associated lipocalin) and IGF-I together with decreased level of IGFBP-3 are associated with pancreatic cancer patients with type 2 diabetes [163]. Accordingly, IGF-I receptor inhibitor LY294002 suppressed the proliferation of several pancreatic cancer cell lines [164].

Some biomolecules have been studied for their potential use in pancreatic cancer immunotherapy. Interestingly, human pancreatic cancer cells engineered to express animal α-Gal epitopes (Galα1-3Galβ1-4GlcNAc-R) can induce strong complement-mediated lysis and antibody-dependent cell-mediated toxicity toward these cells because humans have large quantities of the natural anti-α-Gal antibodies. This strategy can potentially be useful in cancer immunotherapy [165]. For example, Algenpantucel-L vaccine consists of stably transduced human pancreatic cancer cell lines (HAPa-1 and HAPa-2) expressing the murine α(1,3)galactosyltransferase (αGT) gene. In a clinical trial, Algenpantucel-L vaccine improved the survival expectations of patients with pancreatic cancer [166]. Immunizing with cytotoxic T-lymphocyte antigen-4 (CTLA-4) is another novel immunotherapeutic strategy. Ipilimumab, an antibody against CTLA-4, caused tumor regression and improved the clinical manifestations of patients with pancreatic cancer [167].

Conclusions

As our understanding of the human genome increases, specific genetic or genomic information, including DNA sequences and gene expression profiles of mRNA, protein and miRNA molecules, has been used to predict risks and to make treatment decisions for many complex diseases, such as cancer. Variations observed in these sequences and expression profiles in association with disease might help explain why many regulatory and organ systems malfunction, and has prompted the development of new strategies to improve prevention, diagnosis, and treatments. Thus, a new healthcare model, termed personalized medicine, is proposed to tailor medical management and patient care to individual patients by considering their individualized genomic information.

In the case of pancreatic cancer, the fourth leading cause of cancer death in the United States, several alterations of specific oncogenes and tumor suppressor genes as well as of specific miRNAs have been associated with the disease. Specific gene profiles in blood, pancreas tissue, and pancreas juice can potentially be used as new biomarkers for diagnosis, prognosis, and to assess the response to treatment. Many gene alterations that directly contribute to pancreas tumorigenesis have been identified or are under active investigation; therefore it might be possible to develop novel therapies for pancreatic cancer patients targeting specific genes. Accordingly, this type of personalized medicine can be applied to the patient with pancreatic cancer, delivering the right treatment to the right patient, using the right dose at the right time, and when fully implemented it will significantly improve patient management and treatment outcomes.

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