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The Genetics of Pancreatic Cancer

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1. Introduction

Globally, pancreatic cancer is considered a rare cause of cancer. More than 250,000 new cases, equivalent to 2.5% of all forms of cancer, were diagnosed in 2008 worldwide (Ferlay et al., 2008, 2010). Pancreatic adenocarcinoma currently represents the fourth most common cancer causing death in the United States and in most developed countries (Jemal et al., 2009, 2011). Despite advances in medical science, the overall prognosis of pancreatic cancer remains poor and five years survival is only 4% (Jemal et al., 2006). Those diagnosed early, with tumor limited to the pancreas, display a 25-30% five years survival following surgery (Ryu et al., 2010).

It has been suggested that it takes at least 10 years from tumor initiation to the development of the parental clone and another five years to the development of metastatic subclones, with patients dying within two years thereafter, on average (Costello & Neoptolemos, 2011). Given the limited treatment options there has been considerable focus on clinical and molecular harbingers of early disease. A mechanism for early detection and for early intervention remains to be elaborated. Current research is focused on the discovery and the development of diagnostic bio markers that can unveil pancreatic cancer in its early stages. Deciphering and understanding the genetics of sporadic and hereditary pancreatic cancer remains a fundamental milestone.

Based on family aggregation and family history of pancreatic disease, it is estimated that around 10% of cases diagnosed with pancreatic cancer host a hereditary germ line mutation (Lynch et al., 1996; Hruban et al., 1998). Furthermore, it has been observed that pancreatic cancer occurs in excess of expected frequencies, in several familial cancer syndromes, which are associated with specific germ-line mutations. The best characterized include hereditary breast-ovarian cancer syndrome ascribed to mutations in BRCA1/2 genes, especially BRCA2; familial pancreatic and breast cancer syndrome due to mutations in PALB2 gene; familial isolated pancreatic cancer caused by mutations in PALLD encoding palladin; and familial multiple mole melanoma with pancreatic cancer (FAMMM-PC) attributed to

mutations in CDKN2A. Other hereditary cancer syndromes demonstrating increased hereditary risk for pancreatic cancer, yet with less significance, include hereditary non-polyposis colorectal syndrome - Lynch syndrome and Li-Fraumeni syndrome which is caused by mutations in p53 gene.

The identification of individuals at risk for pancreatic cancer would aid in targeting those who might benefit most from cancer surveillance strategies and early detection (Brentnall et al., 1999). This chapter describes the cutting edge data related to the genetics of sporadic and hereditary pancreatic cancer subdivided according to 'genes' function.

2. Oncogenes

2.1 KRAS gene (MIM 190070)

Recent studies have shown that the KRAS oncogene on chromosome 12p is activated by point mutations in approximately 90% of pancreatic cancers tumors, and these mutations involve codon 12 most commonly, and codons 13 and 61 thereafter (Caldas & Kern, 1995). The RAS protein produced by wild-type KRAS binds GTPase-activating protein and regulates cell-cycle progression. Mutations in KRAS constitute the earliest genetic abnormalities underlying the development of pancreatic neoplasms (Maitra et al., 2006; Feldmann et al., 2007). KRAS may thus be a promising bio marker for early detection of curable non-invasive pancreatic neoplasia (Maitra et al., 2006).

2.2 BRAF gene (MIM 164757)

The BRAF gene maps to chromosome 7q and takes part in the RAF–MAP signaling pathway, critical in mediating cancer causing signals in the RAS corridor (Calhoun et al., 2003). BRAF mutations have been described in about 15% of all human cancers, including pancreatic cancer (Davies et al., 2002). The BRAF gene is activated by oncogenic RAS, leading to cooperative mutual effects in cells responding to growth factor signals. BRAF and KRAS appear to be alternately mutated in pancreatic cancers; thus, pancreatic cancers with KRAS gene mutations do not harbor BRAF gene mutations and vice versa (Maitra et al., 2006).

2.3 PALLD gene (MIM 608092)

Palladin RNA is over-expressed in tissues from both precancerous dysplasia and pancreatic adenocarcinoma in familial and sporadic pancreatic disease. The mutated gene is assumingly, best detected in very early precancerous dysplastic tissue, heralding neoplastic transformation before the overarching of genetic instability, underlying cancer, has occurred. Palladin is a component of actin-containing microfilaments that control cell shape, adhesion and contraction and is associated with myocardial infarction and pancreatic cancer. Palladin is most probably a proto-oncogene (Pogue-Geile et al., 2006).

2.3.1 Familial pancreatic cancer associated PALLD gene (MIM 164757)

Few families with isolated pancreatic cancer of early onset and high penetrance have been identified (Lynch et al., 1990; Brentnall et al., 1999; Banke et al., 2000; Hruban et al., 2001;

Meckler et al., 2001). Genomewide linkage screen of a family, noted as 'family X', has shown significant linkage to chromosome 4q32-34 (Eberle et al., 2002). Pogue-Geile et al. (2006) later found a mutation, inducing a proline (hydrophobic) to serine (hydrophilic) amino acid change (P239S), in a highly conserved region of the gene encoding palladin (PALLD), segregating in all affected family members and absent in unaffected family members. Zogopoulous et al. (2007) identified this same mutation (P239S) in one of 84 (1.2%) patients with familial and early-onset pancreatic cancer and in one of 555 controls (0.002%). No evidence for palladin mutations in 48 individuals with familial pancreatic cancer was recorded by Klein et al. (2009). Further investigation is warranted in order to confirm the pathogenecity of mutations in PALLD.

2.4 Other oncogenes

AKT2 (MIM 164731) - It has been suggested that the AKT2 oncogene, on chromosome 19q, contributes to the malignant phenotype of a subset of human ductal pancreatic cancers. Cheng et al., (1996) demonstrated that the AKT2 oncogene is over expressed in approximately 10-15% of pancreatic carcinomas. AKT2 encodes a protein belonging to a subfamily of serine/threonine kinases.

AIB1 (MIM 601937) - AIB1 gene, on chromosome 20q, is amplified in as many as 60% of pancreatic cancers (Anzick et al., 1997; Calhoun et al., 2003; Aguirre et al., 2004). Altered AIB1 expression may contribute to the development of steroid-dependent cancers. It has also been reported that amplification of a localized region on the long arm of chromosome 8 is commonly seen in pancreatic cancers, and this amplification corresponds to the oncogenic transcription factor CMYC (MIM 190080) (Aguirre et al., 2004).

In addition to these genes, numbers of amplicons, amplified from DNA fragments, have been identified in pancreatic cancers by using gene chip technologies (Aguirre et al., 2004). Employing array comparative genomic hybridization (CGH) technology, a high resolution analysis of genome-wide copy number aberrations, permits to identify over expression of DNA fragments in tumor transformed pancreatic cells. Understanding the mechanisms underlying the development of pancreatic cancer may aid target early detection, gene-specific therapies and thereby improve prognosis.

3. Tumor suppressor genes

In pancreatic invasive adenocarcinoma, CDKN2A/INK4A, TP53, and DPC4/SMAD4/ MADH4 are commonly inactivated.

3.1 CDKN2A/INK4A gene (MIM 600160)

The CDKN2A gene on chromosome 9p21 encodes proteins that control two critical cell cycle regulatory pathways, the p53 (TP53) pathway and the retinoblastoma (RB1) pathway. Through the use of shared coding regions and alternative reading frames, the CDKN2A gene produces 2 major proteins: p16(INK4), which is a cyclin-dependent kinase inhibitor checkpoint, and p14(ARF), which binds the p53-stabilizing protein MDM2 (Robertson and Jones, 1999). P16 inhibits cyclin D1 by binding to the cyclin-dependent kinases Cdk4 and Cdk6 thereby causing G1-S cell-cycle arrest (Schutte et al., 1997). Loss of p16 function,

consequent to several different mechanisms, including homozygous deletion, intragenic mutation and epigenetic silencing by gene promoter methylation, is seen in approximately 90% of pancreatic cancers (Caldas et al., 1994; Schutte et al., 1997; Ueki et al., 2000). As a bystander effect, homozygous deletions of the CDKN2A/INK4A gene can also delete both copies of the methylthio-adenosine phosphorylase (MTAP) gene, whose product is essential for the salvage pathway of purine synthesis. In about a third of pancreatic cancers co-deletion of the MTAP and CDKN2A/INK4A genes is observed (Hustinx et al., 2005).

This observation has a potential therapeutic significance, since chemotherapeutic regimes selectively targeted to cells demonstrating loss of Mtap function are currently available.

3.1.1 Familial Atypical Multiple Mole Melanoma – Pancreatic Cancer (FAMMM-PC) syndrome (MIM 606719)

The association between mutations in p16 (CDKN2A) and familial pancreatic cancer was previously noted by Caldas et al. (1994) and others (Liu et al., 1995; Whelan et al., 1995; Schutte et al., 1997). Further evidence for a plausible role of CDKN2A in pancreatic cancer was provided by Whelan et al. (1995) who described a kindred at risk for pancreatic cancers, melanomas, and additional types of tumors, co-segregating with a CDKN2A mutation. CDKN2A mutations were detected individuals with pancreatic cancer from melanoma families (Goldstein et al., 1995). Later, Lynch et al., 2002, coined the term hereditary FAMMM-PC syndrome to describe families with both melanoma and pancreatic cancers. Although rare, the life time risk of CDKN2A carriers, to develop pancreatic cancer and melanoma was calculated to be 58% and 39%, respectively (McWilliams et al., 2010). Basically, CDKN2A is a small gene, containing 3 coding exons. However, lack of founder mutations impedes the screening of families at risk in the clinical setting.

3.2 TP53 gene (MIM 191170)

The TP53 gene on chromosome 17p undergoes bi-allelic inactivation in approximately 50–75% of pancreatic cancers, almost always subject to the combination of an intragenic mutation and the loss of the second wild-type allele (Redston et al., 1994). The transcription factor p53 responds to diverse cellular stresses formulated to regulate target genes participating in G1-S cell cycle checkpoint, maintenance of G2-M arrest, cell cycle arrest, apoptosis, senescence and DNA repair (Redston et al., 1994). There is emerging evidence to suggest that loss of p53 function may contribute to the genomic instability observed in pancreatic cancers (Hingorani et al., 2005); and that TP53 gene mutations constitute late events in pancreatic cancer progression (Maitra et al., 2003).

3.2.1 Li- Fraumeni syndrome (MIM 151623)

Li-Fraumeni syndrome is a rare, clinically and genetically heterogeneous, inherited cancer syndrome caused by germline mutations in TP53. Li-Fraumeni syndrome is characterized by autosomal dominant inheritance and early onset of tumors, rather multiple tumors in one individual and multiple affected family members. In contrast to other inherited cancer syndromes, which are predominantly characterized by site-specific cancers, Li-Fraumeni syndrome presents with a variety of tumor types. The most common types are soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical

carcinoma (Li et al., 1988). Several families with Li-Fraumeni syndrome presenting with pancreatic cancer were occasionally described (Lynch et al., 1985; Casey et al., 1993).

3.3 Deleted in pancreatic carcinoma 4 (DPC4) gene (MIM 600993)

About 90% of human somatic pancreatic carcinomas show allelic loss at 18q. Hahn et al. (1996) reported the identification of a putative tumor suppressor gene, namely, Deleted in Pancreatic Carcinoma 4 or DPC4 (also known as SMAD4/MADH4) on chromosome 18q21.1. Loss of Dpc4 protein function interferes with intracellular signaling cascades leading to decreased growth inhibition and uncontrolled proliferation. SMAD4 plays a pivotal role in signal transduction of the transforming growth factor beta superfamily cytokines by mediating transcriptional activation of target genes. Immunohistochemical labeling for Dpc4 protein expression mirrors DPC4/SMAD4/MADH4 gene status with rare exceptions, and like TP53, loss of Dpc4 expression is a late genetic event in pancreatic carcinoma and is observed in about 30% of progression lesions (Feldmann et al., 2007).

Genome-wide association studies (GWAS) have provided evidence that a person's risk of developing pancreatic cancer is influenced by multiple common disease alleles with small effects (Low et al., 2010; Petersen et al., 2010). Further research is required to evaluate the epidemiological input of these markers to the development of pancreatic cancer and their availability for early detection (Costello & Neoptolemos, 2011). Other tumor-suppressor genes are targeted at low frequency in pancreatic cancer. These genes provide a significant insight unto the molecular mechanism that underlines pancreatic cancers, and may serve as therapeutic targets in the early stages of pancreatic cancer.

4. Genome-maintenance genes

Several gene ensembles, that play a role in caring for genome stability, were found to be mutated in pancreatic cancer, more so, in familial rather than sporadic cancer, including familial pancreatic cancer. BRCA2 is with no doubt the prominent gene in this category.

4.1 BRCA1/2 genes (MIM 113705/600185)

BRCA1 - The gene product of BRCA1, functions in a number of cellular pathways that maintain genomic stability, including DNA damage-induced cell cycle checkpoint activation and arrest, DNA damage repair, protein ubiquitination, chromatin remodeling, as well as transcriptional regulation and apoptosis (see for example review by Wu et al., 2010). BRCA1 forms several distinct complexes through association with different adaptor proteins, and each complex assemble in a mutually exclusive manner (Wang et al., 2009).

BRCA2 – BRCA2 plays a key role in recombinational DNA repair, maintenance of genomic integrity and resistance to agents that damage DNA or collapse replication forks. The role of BRCA2 is best understood during DNA double-strand break repair (see for example Schlacher et al., 2011) as it co-localizes with PALB2 gene in nuclear foci, thereby promoting its stability in nuclear structures and enabling its recombinational repair and checkpoint functions (Xia et al., 2006).

Both BRCA1 and BRCA2 have transcriptional activation and seem to be mutually interrelated.

Traditionally BRCA1 and BRCA2 were classified as tumor suppressor genes. Nowadays, BRCA1 and BRCA2 are rather cataloged as 'caretaker' genes that act, amongst other, as nucleotide-excision-repair (NER) genes (Kinzler and Vogelstein, 1997). While, inactivated 'gatekeepers', namely, tumor suppressor genes, promote tumor initiation directly, the inactivation of caretaker genes leads to genetic instability resulting in increased mutations in other genes, including gatekeepers. Once a tumor is initiated by inactivation of a caretaker gene, it may progress rapidly due to an accelerated rate of mutations in other genes that directly control cell birth or death. Consistent with this hypothesis, mutations in BRCA1 and BRCA2 are rarely found in sporadic cancers, and the risk of cancer arising in people with BRCA somatic mutations is relatively low.

4.1.1 Hereditary breast-ovarian cancer syndrome

Since the late nineties of the 20th century, excess of pancreatic cancer cases was documented in families with hereditary breast-ovarian cancer syndrome, traditionally linked to BRCA1/2 genes. Several studies have shown high BRCA2 mutation carrier frequencies in pancreatic cancer patients, reaching 10-20%, more so in Jewish Ashkenazi compared to non-Jewish pancreatic cancer patients (Teng et al., 1996; Ozcelik et al., 1997; Slater et al., 2010), with greater penetrance for males over females (Risch et al., 2001; Murphy et al., 2002; McWilliams et al., 2005; Dagan, 2008; Dagan et al., 2010; Ferrone et al., 2009). BRCA1 mutations are less often associated with pancreatic cancer compared to BRCA2 mutations (Al-Sukhni et al., 2008; Dagan et al., 2010). Mutations within the OCCR-ovarian cancer-cluster region of the BRCA2 gene in exon 11 frequently cause either/or pancreatic cancer, ovarian cancer and other type of cancers (Risch et al., 2001; Thompson et al., 2001).

The distinction between gatekeepers and caretakers genes has important practical and theoretical ramifications. Tumors that have defective caretaker genes are expected to respond favorably to therapeutic agents that induce the type of genomic damage that is normally detected or repaired by the particular caretaker gene involved.

Poly (ADP-ribose) polymerase (PARP) inhibitors have raised recent excitement as to their deleterious effect on BRCA1 or BRCA2 associated ovarian, breast or pancreatic cancer cells. If either PARP or BRCA function remains intact, a cell will continue to survive. Thus, inhibiting PARP should not affect the non-cancerous cells that contain one functional copy of BRCA. Loss of both functions, however, is incompatible with life (Bryant et al., 2005; Helleday et al., 2005; Drew et al., 2011). With this in mind, this class of agents has the potential to potentiate cytotoxic therapy without increased side effects. Acting as sole agents, they are able to exterminate cancer cells with DNA repair defects. The genomic instability of tumor cells allows PARP inhibitors to selectively target tumor cells rather than normal cells. PARP proteins inhibitors have gained supremacy as ideal anticancer agents (Weil & Chen, 2011) and may promise better prognosis in pancreatic, ovarian and breast cancer due to hereditary mutations in BRCA1/2.

4.2 Partner and localizer of BRCA2 (PALB2) gene (MIM 610355)

PALB2 maps to chromosome 16p12 (Xia et al., 2006; Reid et al., 2007; Xia et al., 2007). Differential extraction showed that BRCA2 and PALB2 colocalize in S-phase foci and are associated with stable nuclear structures. As PALB2 is critical for the function of BRCA2 as

regards DNA repair, it should be considered, in principle, as a caretaker gene. Like BRCA2, PALB2 participates in DNA damage response and both genes collectively cooperate allowing BRCA2 to escape the effects of proteasome-mediated degradation (Reid et al., 2007; Xia et al., 2007).

4.2.1 Familial pancreatic cancer associated PALB2

Germline mutations in PALB2 have been identified in approximately 1-2% of familial breast cancer and 3-4% of familial pancreatic cancer cases (Slater et al., 2010; Casadei et al., 2011; Hofstatter et al., 2011). Three pancreatic cancer patients out of 96, with a positive family history of pancreatic cancer were found to harbor a PALB2 germline deletion of 4 basepairs, that was absent in 1084 control samples (Jones et al., 2009; Rahman et al., 2007). PALB2 appears to be the second most commonly mutated gene implicated in hereditary pancreatic cancer after BRCA2 (Jones et al., 2009).

4.3 Hereditary non-polyposis colon syndrome – HNPCC (MIM 120435)

Pancreatic cancer was infrequently described in families with hereditary non-polyposis colon cancer (Lynch et al., 1985; Miyaki et al., 1997). HNPCC subdivided into Lynch I, primarily affecting the colon, Lynch II mainly targeting extra colonic organs including the pancreas and Muir-Torre syndrome. HNPCC is a genetically heterogeneous disease, with most mutations detected in MSH2 and MLH1 genes.

MSH2 (MIM 609309) - The microsatellite DNA instability that is associated with alteration in the MSH2 gene in hereditary nonpolyposis colon cancer and several forms of sporadic cancer is thought to arise from defective repair of DNA replication errors. MSH2 has a direct role in mutation avoidance and microsatellite stability in human cells (Fishel et al., 1994).

MLH1 (MIM 609310) – Similarly to MSH2, MLH1 gene encodes a protein involved in the identification and repair of DNA mismatch errors. The identification of germline mutations in *MLH1* and *MSH2* was rapidly followed by the discovery of other human genes that encode proteins involved in the mismatch repair (MMR) complex (see review by Lynch et al., 2009).

5. Synopsis

Pancreatic cancer is of the most lethal of all human malignancies caused by inherited and acquired (somatic) mutations. The poor prognosis of pancreatic cancer (Jemal et al., 2006) warrants early detection of asymptomatic individuals, at high risk, using imaging methods and molecular analyses and thereby providing them with a chance for better survival (Goggins et al., 2000). Understanding the complex genetic mechanisms underlying the development of pancreatic cancer, as depicted in this chapter, may conduit medical science in the path that will ultimately lead to early detection, tailored treatment and consequently better prognosis for this incurable disease.

Although, novel mechanisms, sprout on the horizon, could be exploited for early detection, as depicted by the KRAS detection technology, it seems that most pancreatic neoplasms in the general population will remain undetectable before invasive cancer develops. However, the recognition of early genetic somatic changes can advocate for presymptomatic chemo or

surgical prevention schemes that may alleviate those with pre cancerous neoplasms before an invasive cancer had a chance to develop. This farfetched undertaking is already underway.

Although, pancreatic cancer is basically sporadic, about 10% of the patients harbor a germline mutation. It seems that BRCA2 is the major susceptibility gene contributing to hereditary pancreatic cancer, especially in populations segregating founder mutations, namely, Ashkenazi Jews, Icelandic (Thorlacius et al., 1996; Dagan, 2008; Dagan et al., 2010) and others. Beyond this, pancreatic cancer patients and family members at risk should follow the standard recommendations, as regards genetic counseling and diagnosis that befits hereditary breast-ovarian cancer. Thus, the follow-up surveillance schemes for BRCA1/2 mutation carriers have to focus, in addition to the standard recommendations, on early detection of pancreatic cancer.

Deciphering the precise functional role of genes, involved in the development of pancreatic cancer, may open new and exciting targets for chemotherapy. The recognition that BRCA1/2 and PARP proteins combine forces in maintaining genomic stability and DNA damage repair, as well as transcriptional regulation and apoptosis, has prompted the clinical development of PARP inhibitors. It has been recently shown that PARP inhibitors are selectively toxic to human cancer cell lines with BRCA1/2 mutations. Furthermore, these agents may have a therapeutic potential in tumors with defects in homologous recombinant DNA repair (HRR) system (Drew et al., 2010). Clinical trials of PARP inhibitors, especially with olaparib, in BRCA1/2 mutated cancer patients confirm their potential therapeutic effect. Further studies are required to address the many questions regarding safety and efficacy in the clinical setting (Fong et al., 2009).

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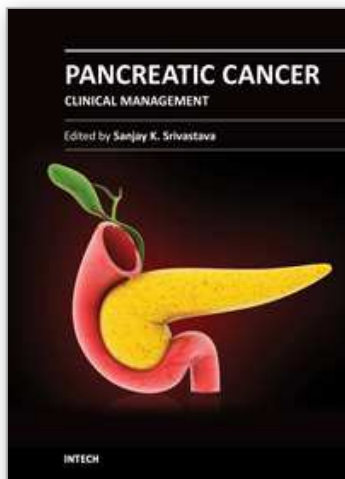
Pancreatic Cancer - Clinical Management

Edited by Prof. Sanjay Srivastava

This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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