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Molecular Pathology of Pancreatic Adenocarcinoma: A Review

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ABSTRACT: The etiology of cancer is very complex and yet to understand thoroughly. One of the most complex type of them is pancreatic cancer, especially Pancreatic Adenocarcinoma which is also the most common form of pancreatic cancer. Researchers have shown that specific gene mutations are the initial footstep of this form of cancer, for example inactivation of tumor-suppressor genes such as p16, DPC4, and p53, or activation of oncogenes such as K-ras, are a few of the mutations that trigger the growth of Pancreatic Adenocarcinoma. Although there could be many other aspects of molecular crosstalk that can help in promotion and progression of it. miRNAs and Epigenetic modifications also play an important role in the progression of pancreatic cancer. Several tumor suppressor genes can be silenced due to hypermethylation of CpG island in promoter region. Other studies indicate the involvement of miRNAs in the regulation of cell proliferation and apoptosis, as well as their altered expression in pancreatic cancer. This review tried to give an overlook on the molecular pathogenesis of pancreatic adenocarcinoma at different level of molecular interactions.

Keywords: Pancreatic Adenocarcinoma; Gene mutation; Epigenetic modification and miRNAs.

INTRODUCTION: Pancreatic Adenocarcinoma is one of the most common forms of pancreatic cancer and at the same time one of the most challenging form of human malignancies (1-2). For the past two decades it is known that pancreatic adenocarcinoma is caused, at least in part, by genetic alterations to some specific protein-coding oncogenes and tumor suppressor genes such as KRAS, INK4A and SMAD4 (3-7). These alterations result mainly from somatic genetic events such as mutations. Although it is clear that pancreatic cancer is initiated by genetic mutations, it is also evident that in many cases tumor shows alterations in the expression of tumor suppressor genes because of epigenetic alterations such as the methylation of CpG islands in their promoters that lead to loss of function. Over the past few years, many miRNAs have also been implicated in pancreatic cancers. Both losses and gains of miRNA function have been shown to contribute to pancreatic cancer development through a range of mechanisms. In short, genetical, epigenetical and miRNA mediated loss or gain of functions of various gene (or its products) togetherly contribute to initiation and progression of pancreatic adenocarcinoma. Here in this review the author made an effort to give a short overview of the etiology of pancreatic adenocarcinoma in the light of modern research.

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A. GENETIC ALTERATION: All form of pancreatic cancer including pancreatic adenocarcinoma is primarily a genetic disease and the very first reason of carcinogenesis is often found to be mutation, amplification and deletion of various genes. In some cases mutations cause hyper-activation of the gens known as activation mutation, while on the other side some genes are become inactivated or suppressed due to mutations and these mutations called as inactivation mutations, For example, mutations causing activation of the *KRAS* oncogene along with inactivation of several tumor suppressor genes such as *p53, p16* and *SMAD4* are most common in pancreatic cancer.

It has been found that mutation frequencies for *p16*, *p53*, and *KRAS* are approximately 80, 70, and 90%, respectively in case of pancreatic cancer. Also, the functional relevance of such mutations in the context of pancreatic adenocarcinoma is extremely important (4-11).Though mutations of some gene are the most prominent step to begin the process of pancreatic adenocarcinoma formation yet it has been found that many genes or chromosomal segments are either deleted or amplified in this deadly disease and may play very significant roles in development of the same (12). Thus, both the types of genetic alterations are equally important and lead to formation of pancreatic cancer. The role of the specific genes which are found to be associated with pancreatic adenocarcinoma formation and progression are been discussed below.

KRAS: The *KRAS2* or simply K*RAS*gene (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) is an oncogene that encodes a small GTPasetransductor protein called K*RAS* protein. The RAS group of proteins function as a part of the membrane-associated, signal-transduction pathway of GTP-binding proteins. Once activated, these proteins code for key mediators in a number of pathways regulating cell survival, growth and differentiation. K*RAS* is involved in the regulation of cell division as a result of its ability to relay external signals to the cell nucleus. Generally it remains in inactive state unless an external signal such as growth factor activates the protein. Once activated KRAS can further elicit downstream signaling that ultimately activate the proteins related to cell growth, differentiation, and survival directly.

K*RAS* mutations are found in approximately 90% of pancreatic cancers. Mutations in this oncogene have been found in all degrees of ductal anaplasia (i.e. reversion of differentiation process and attaining the characteristic of malignant tumors of cells, here epithelial cells) and these alterations are considered to be early events in tumorigenesis. *RAS* mutations involve only certain amino acids, those which interfere with the GTPase function. In pancreatic cancer, mutations are mostly found at the twelfth position, (codon or amino acid 12), with exceptions seen at codon 13 or 61. Most mutations in pancreatic cancer change a glycine (at codon 12) to a valine or aspartate and they become more active in signaling. Activating mutations in the *KRAS* gene impair the ability of the *KRAS* protein to switch between active and inactive states, leading to cell growth proliferation and increased resistance to chemotherapy. It is also found that constant active mode of *RAS* results in aberrant activation of proliferative and survival signaling pathways (13-17).

INK4A/p16: Cyclin-dependent kinase inhibitor 2A (commonly known as CDKN2A or p16Ink4A or just p16) is a tumor suppressor 16 Kda protein, which is encoded by the CDKN2A gene in humans.p16 plays very important role in regulating the cell cycle, and mutations in p16 increase the risk of developing a cancers. Inactivation of the p16 dependent tumor-suppressive pathway is an important mechanism of development of many human cancers including pancreatic cancer (18-20). This pathway has been well-studied so far as a part of global cell cycle regulation and inactivation of this pathway may occur through alterations of different members of the pathway including Rb, *CDK4*, *cyclin D*, or *p16*. The p16 protein inhibits formation of cyclin D/CDK4 complexes during progression of cell cycle and hence under normal circumstances provides a stop signal to the process of cell division at G1/S check point if any assault of DNA being detected. Hence, loss of function of p16 results in the release of activated transcription factors and progression of the cell cycle through the G1/S checkpoint (21-22). In general, about 95% of all tumors have inactivation of the CDKN2A gene, with the loss of the p16 protein and an increase in cell proliferation.

A number of studies suggest a significant role of *p16* inactivation in development of pancreatic adenocarcinoma. Initially *p16* mutations in 50% and homozygous deletions in 30% of 10 human pancreatic cancer cell lines were being identified. Moreover, the identification of frequent deletions (41%) and mutations (38%) in primary pancreatic tumor specimens indicated that these changes were more likely associated with the process of pancreatic carcinogenesis. Studies indicate that these genetic events have functional significance too. A significantly increased risk of pancreatic cancer in melanoma-prone kindred fami-

lies with *p16*mutations lends further support to the role of *p16* abrogation in human pancreatic carcinogenesis. Many recent studies have demonstrated that transfection of wild-type *p16* into human pancreatic cancer cells results in decreased tumor cell proliferation in vitro and in vivo. Clinical studies on human subjects with pancreatic adenocarcinoma had evaluated *p16* status further. Significantly greater frequency of *p16* alterations was found in the short-term survivors when compared to the long-term survivors (85% versus 50%). Taken together all these studies have proven the fact that p16 mutation has got a vital role to play in initiation and progression of pancreatic adenocarcinoma. In a study, Caldas et. al. found that allelic deletions of 9p21−p22 in 85% of pancreatic adenocarcinomas. Further Analysis of MTS1 in pancreatic carcinomas (27 xenografts and 10 cell lines) showed homozygous deletions in 15 (41%) and sequence changes in 14 (38%). (23-28)

p53: p53 (alternatively known as “protein 53” or “tumor protein 53”) is a tumor suppressor protein which is encoded by the *TP53* gene in human. In general, p53 protein responds to cellular DNA damage. It blocks the progression of cells through the G1 phase of the cell cycle. The protein is also capable of mediating cell death, or apoptosis, by detecting irreversible DNA damage within a cell. Abnormal p53 permits cells to bypass DNA damage control mechanisms and apoptotic signals and hence, restore genomic instability in cells. In pancreatic cancer, the primary mechanism of *p53* inactivation seems to be mutation (29).*TP53* is ubiquitously expressed in mutated forms in many different types of human carcinomas and is inactivated in upto 75% of pancreatic cancers. Mutated p53 proteins have been shown to inhibit wild-type p53, and bi-allelic inactivation may not be necessary for loss of function. In human pancreatic adenocarcinoma, mutated p53 accumulation significantly correlates with promotion of metastatic property of the same. p53 is also associated with *K-RAS*mutations suggesting a cooperative effect in pancreatic tumorigenesis (30). It has been found that p53 inactivation is a late event in pancreatic adenocarcinoma formation. Once p53 is inactivated it cannot detect the DNA damage can is unable to stop cell cycle progression and hence cells proceed further with DNA damages giving rise to further genetical changes within the cells. This leads to more aggressive stage of the cancer.

Another cause of p53 inactivation in pancreatic cancer is its deletion. Cancer cell form patients samples are been detected with p53 deletion in more than 50 percent of cases. A recent study revealed that p53 deletion detected by fluorescent in situ hybridization in peritoneal drainage fluid is correlated with early peritoneal seeding in resectable pancreatic cancer. Scientists also suggested that patients with p53 deletion in peritoneal drainage fluid need more aggressive adjuvant treatment. In vivo study using mouse model also support the fact and shows that p53 deletion is associated with metastatic potential of pancreatic adenocarcinoma cells. (31-34)

SMAD4/ DPC4: Smads, intracellular proteins that transduce extracellular signals from transforming growth factor beta TGFβ ligands to the nucleus, are known to be as tumor suppressors after they were been discovered and characterized. SMAD4, also termed as Deleted in Pancreatic Cancer, locus 4 (DPC4) or *DPC*4 gene, was originally isolated from human chromosome 18q21. SMAD4 deletion and mutation is very common in patients with pancreatic cancer and it is also a late event in pancreatic carcinogenesis (35). The functional role of SMAD4 in pancreatic cancer has yet to be understood, but it has been shown that approximately 50 to 55% of pancreatic cancers bear deletions or mutations in SMAD4/DPC4. Patients with pancreatic cancer are been reported with about 30% homozygous deletion and 20%-25% mutation of SMAD4. Studies have also demonstrated that inactivation of *DPC*4 in murine intestinal neoplasms is associated with more invasive growth (36-37). Loss of *DPC4* resulting in aberrant signaling by the transforming growth factor β (TGF-β) cell-surface receptor. Reports suggest that in pancreatic cancer, Smad4 loss cannot initiate tumor formation but promotes metastases. Patients with intact SMAD4 gene have been shown to survive 5-years or more after diagnosis of pancreatic cancer.Mutations in SMAD4 gene are often found in the C-terminal MH2 domain, which represents a mutational hotspot corresponding to codons 330-370, known as mutation cluster region.The mutant protein cannot be recruited to DNA by transcription factors and hence cannot form transcriptionally active DNA-binding complexes. These common mutations cause C-terminal truncation of SMAD4 which ultimately leads to decreased stability. Mutant Smad4 protein neither forms homomeric complex nor the heteromeric complex with Smad2. Actually the process of truncation removes residues critical for homomeric and heteromericSmad complex formation. This phenomenon is linked with initial stages of adenocarcinoma formation, whereas deletion of Smad4 occurs at later stages of pancreatic cancer. Total loss of Smad4 protein expression correlated with the pres-

ence of widespread metastasis but not with locally destructive tumors. Hence it is a very significant and prominent role in progression of pancreatic adenocarcinoma (38-47).

BRCA2: Mutations causing its suppression in the tumor suppressor genes *breast cancer antigen gene* (*BRCA*) 1 and 2 have been proven to drastically increase risk of breast and ovarian cancers in the individuals who carry them, but studies have shown that the next most common cancer associated with BRCA mutations is pancreatic cancer. A study found that the risk of pancreatic cancer is approximately doubled in female who are mutated BRCA carriers. Hence, BRCA gene mutation could be an additional risk factor for development of pancreatic cancer. Another study investigated the germline mutations in BRCA1/2 related to pancreatic cancer and estimated the incidence of pancreatic cancer in a cohort of female carriers of BRCA1 and BRCA2 mutation and their conclusion was in corroboration with previous studies. (48-52)

HER2/ERBB2: Epidermal growth factor receptor-2 (HER-2) has been implicated in malignant transformation of different type of cancer. A study on pancreatic cancer showed HER2 gene to be amplified in 12 out of 27 (44%) tumors detected by real time PCR. But HER-2 gene amplification data in pancreatic cancers did not correspond with the immunohistochemical detection. There are conflicting reports as to the significance of HER2 gene amplification in pancreatic cancer. Another study found HER2 gene amplification in 16 cases out of 63 cases of resected pancreatic cancer (25%). But no statistical significance was found between the genetic parameters and tumor characteristics, stage, or survival (53).

Other genes: *Myb* gene is known to be amplified in about 10% of pancreatic cancer. In a recent study, aimed to identify chromosomal aberrations in pancreatic cancer tissues, amplification on 6q was being detected. The c-myb proto-oncogene was found to be amplified in 10% of the pancreatic carcinoma tissues. Amplification of c-myb was mainly found in advanced tumors which indicate correlation to progression and malignant properties of pancreatic adenocarcinoma tumors.

RAF is a member of effector pathway of RAS. One of the family members of RAF is BRAF which is also considered to be a proto-oncogene. It is located on chromosome 7q. BRAF and KRAS mutations are found to be mutually exclusive in pancreatic cancer. V600E mutation in BRAF substitutes an amino acid at position 600, from a valine (V) to a glutamic acid (E). Reports are available on the correlation of this mutation of BRAF with pancreatic cancer. It was showed that more than 99% of the earliest-stage, lowest-grade,pancreatic intraepithelial neoplasm-1 lesions contain mutations in KRAS, p16/CDKN2Aor in BRAF but cancer with KRAS mutations do nor harbor BRAF mutations. A study from Collisson et al. shows that BRAF(V600E) can create pancreatic intraepithelial neoplasia (PanIN) lesions in mouse model. Moreover, scientists have established the fact that concomitant expression of BRAF(V600E) and TP53(R270H) result in lethal pancreatic adenocarcinoma.

Phosphatase and tensin homolog (*PTEN*) is a protein thatnegatively regulatesAkt/PKB signaling pathway and is encoded by the PTEN gene. PTEN is considered to be a very important tumor suppressor gene. It has been found that *PTEN* is deleted or downregulated in human pancreatic cancer, and *PTEN* inactivation cooperates with $KRAS^{G12D}$to induce PDAC.

Rbencodes a cell-cycle regulator that is functionally disrupted in most human cancers including pancreatic ductal adenocarcinomas. Recently it was found that deletion of Rb accelerates pancreatic carcinogenesis by with the help of *KRAS*. (54-59)

B. EPIGENETIC MODIFICATIONS: In addition to the widespread genetic alterations, it is now known that epigenetic mechanisms are also important in developing different type of human cancers. Pancreatic cancers are known to harbor more than one type of epigenetic alterations such as DNA methylation and histone modification. In this section the epigenetic alterations associated with pancreatic adenocarcinoma has been discussed.

DNA methylation: DNA methylation occurs by addition of a methyl group to the 5′ position of cytosine of palindromic dinucleotide, CpG. This change is occurred by a family of DNA methyl-transferases (DNMTs) which includes DNMT1, DNMT3a and DNMT3b. DNMT1 overexpression has been described in certain cancers and in this context scientists have found that in many cases pancreatic cancers harbor overexpression of DNMT1. Alterations in CpG island methylation in pancreatic cancer has been found in many studies, for example some suppressor genes show aberrant promoter CpG island hypermethylation in pancreatic cancers. One of the most important tumor suppressor genes shown to undergo promoter hypermethylation and gene silencing is the

p16/CDKN1A gene. Similarly, some classic tumor suppressor genes and DNA repair genes that are mutated in other cancers have been shown to undergo epigenetic silencing in pancreatic cancers as well. Cyclin-dependent kinase inhibitor, CDKN1C/p57KIP2 is a potent inhibitor of several G1 cyclin complexes and is a negative regulator of cell proliferation. Partial methylation of the CDKN1C promoter CpG island is commonly observed in pancreatic cancer cell lines with reduced CDKN1C expression. Another gene commonly silenced epigenetically in pancreatic cancer is BNIP3. Silencing of BNIP3 was associated with CpG island methylation in the region of the transcription start site. (60-62)

Histone modification: Histone Modifications in pancreatic cancer is another aspect of epigenetical regulation of the carcinogenesis. Histones are globular proteins with protruding N-terminal tails that are themain site of biochemical modifications including acetylation, methylation, phosphorylation, and ubiquitination. In pancreatic cancer genes of the mucin family have been shown to undergo histone alterations followed by gene overexpression. On an addition, several microRNAs (miRs) have been identified that are regulated by DNA methylation in pancreatic cancer. Noncoding RNA such as miRs and natural antisense transcripts (NATs) are known to be involved in post-transcriptional gene silencing (PTGS). For example, certain miRs regulate DNA methylation. miR-29 inhibits DNMT3 activity and transfection of miR-29 into miR-29 negative cell lines inhibits DNA methylation. (60-63)

C. FUNCTIONAL ALTERATION OF GENE: Genes are also been found to be functionally altered in pancreatic cancer**.** Here we discuss some of the functionally hypo or hyper active gene product and its association with pancreatic cancer.

1. Growth factor receptors:

EGFR: Epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein which is a member of the tyrosine kinase family of growth factors receptors and is encoded by proto-oncogenes. Several studies have demonstrated that EGFR is over-expressed in pancreatic cancer. Over-expression correlates with more advanced disease, poor survival and the presence of metastases. The EGFR is present on the short arm of chromosome 7 (7p). Increased expression of EGFR in human pancreatic cancer can be associated with either structural or numerical alterations of chromosome 7. EGFR is encoded by the *ERBB-1* proto-oncogene. In normal pancreas, c-ERBB-1 is expressed only in the islets of Langerhans. Nevertheless, the *ERBB-1* gene is over expressed in human pancreatic cell lines in up to 85% of ductal adenocarcinomas, due to gene amplifications. Recently, studies have shown EGFR amplification and overexpression in pancreatic cancer and the expression was correlated with local advanced and metastatic stage of disease. Over-expression of epidermal growth factor receptor (EGFR) was suggested to be associated with malignant transformation of pancreatic cancer. GFR immunoreactivity was detected in 41.6% (32/77) of human pancreatic cancers. Scientific observations suggest that EGFR expression plays important roles in metastasis of human pancreatic cancer.

HER2: Blocking of overexpressed HER2 oncogene improves survival in breast and gastroesophageal cancer however its role in pancreatic adenocarcinoma is inconclusive. Studies found that HER2 is overexpressed in a subset of PDACs, identifying them as possible candidates for a targeted therapy. In another study, for the purpose of determining the prognostic significance of HER2/neu oncogene in pancreatic cancers, 21 pancreatic cancers of ductal origin were studied immunohistochemically using the monoclonal antibody (MAb) CB11, specifically reactive with HER2/neu product. Staining of the epithelium of the normal duct was negative or weakly positive. Moderately and strongly positive reactions indicated the overexpression of this gene, and were found in 47.6% pancreatic cancers of ductal origin. Overexpression of HER2/neu was also found to be closely and inversely related to the survival of the patients with pancreatic cancer of ductal origin.

TGFβ: The role of TGF-β pathway in cancer is somewhat contradictory. This pathway can inhibit cell proliferation and suppress cancerous transformation by modulating expression of cell-cycle regulators. On the other hand, TGF-β can promote malignant growth through multiple mechanisms including enhanced cancer cell invasion, survival and matrix remodeling.TGF-β pathway function in pancreatic ductal adenocarcinoma (PDAC) is very complex. As discussed earlier, inactivation of SMAD4 and other pathway components are present in approximately 50% of human PDAC and cooperate with activated Kras to promote PDAC. However, TGF-β ligands are commonly overexpressed in PDAC, and can promote epithelial-to-mesenchymal transition (EMT) and invasion of cancer cells. TGF-β can also induce angiogenesis,

activate tumor-promoting myofibroblasts (stellate cells), and attenuate immune surveillance.

Reports suggest that pancreatic cancers overexpress transforming growth factor beta (TGF-β). The presence of TGF-beta 1, TGF-beta 2 and TGF-beta 3 in pancreatic cancer was been demonstrated immunohistochemicallylong back. The presence of TGF-beta 2 was found to be associated with advanced tumor stage. Findings of Friess et al. show that human pancreatic cancers have increased levels of TGF-beta isoforms that suggest the presence of TGF-beta in pancreatic cancer cells may contribute to disease progression.

More recently, overexpression of transforming growth factor-beta 2 (TGF-β2) in pancreatic malignancies is found to have a pivotal role in malignant transformation and progression. Thus overexpression of this growth factor is associated with pancreatic cancer progression. (54-59)

2. Cytokines and Chemokines: Cytokines also play important role in progression of a wide range of tumors. Cytokines, upon produced locally, interacts with the microenvironment of tumor or tumor cells and often help them to survive and reciprocate or invade within the surrounding tissues. A study focused on the expression of different cytokines both in vitro and in patient samples revealed overexpression of IL-1b, IL-6, IL-8, IL-10, IL-11, IL-12 p40, IL-18, IFN-c, TGF-b1, TGF-b2 and TGF-b3 at the mRNA level and IL-1b, IL-18, TGF-b2 and TGF-b3 also at the protein level.Furthermore, cytokineswere also measured in supernatants and sera (from patients) in the same study showing presence of IL-1b, IL-6, IL-10, IL-11 and IL-12 as soluble proteins in supernatants.This finding illustrates the probable role of cytokines in pancreatic cancer progression. Another study found significantly higher levels of TNF-alpha, IL8 and IL6 in from sera of pancreatic adenocarcinoma patients compared to healthy controls.

In the year 2003, Kuwadaet. al. conducted a study to examine the expression of IL-8 and IL-8 receptors in human pancreatic cancer. They examined the expression of IL-8 and its two receptors (CXCR1 and CXCR2) in 40 surgically resected human pancreatic cancer tissues and in some cell lines. They found positive staining for IL-8, CXCR1 and CXCR2 in surgically resected human pancreatic cancer was 50, 55 and 65%, respectively. They also validated their results in in vitro. Hence it can be stated that IL-8 and IL-8 receptors are over-expressed in pancreatic cancer.Other reports suggest that IL8 along with CXCL12 can cooperatively promote angiogenesis and invasive property of pancreatic cancer cells.

Recently, Qin et al have investigated the expression of IL-8 and its receptor CXCR1 by immunohistochemistry in pancreatic cancer and chronic pancreatitis samples and they found that IL-8 and CXCR1 proteins were both over-expressed in pancreatic adenocarcinoma samples (55.6% and 65.4%, respectively) compared with the matched para-cancer tissues.

Certain chemokine receptors have also been found to play very significant role in tumor growth and development, among them CXCR4 has been linked to tumor progression in diverse tumor entities. In a study CXCR4 expression of pancreatic cancer was retrospectively assessed by immunohistochemistry in 103 patients with pancreatic cancer. Intensity of CXCR4 expression was correlated with both tumor and patient characteristics. Strong CXCR4 expression was significantly associated with stages of advanced pancreatic cancer (64-69).

D. MicroRNAs: Genome-wide profiling shows that alterations in miRNA expression were not rather common in human cancer. Not many works have been published specifically dealing with pancreatic cancer and miRNA profiling. The principal goal of such studies is to identify gene signatures for early prognosis, progression or for disease outcome. Attempts were made to characterize the miRNA expression in pancreatic adenocarcinoma. In a study, the authors identified miRNAs specifically over expressed in pancreatic adenocarcinoma such as miR-376a, miR-301, miR-155, miR-21, miR-221 and miR-222. Two miRNAs located on chromosome 17p13 (miR-132 and miR-212) have been recently reported to be overexpressed in pancreatic cancer as compared to normal pancreas. It has been reported that miR-96 is downregulated in pancreatic cancer as compared to normal tissues and targets KRAS. Restoring miR-96 expression strongly inhibited in vitro cell proliferation, invasion and induced apoptosis. The miRNA miR-34a, which is directly regulated by p53, is subjected to epigenetic silencing in numerous neoplasms, including pancreatic cancer.

In another report it has been identified that 11 differentially expressed miRs differentiating pancreatic cancer from either normal pancreas or chronic pancreatitis. One of them, miR-21, has been suggested as a biomarker for disease outcome because it is overexpressed in pancreatic cancer. Recently, results from a study showed that tumors from patients demonstrating elevated expression levels of four miRs (miR-155,

miR-203, miR-210 and miR-222) possessed a 6.2-fold increased risk of tumor-related death compared with patients whose tumors showed a lower expression of these miRs. Moreover eight miRs were significantly upregulated in most pancreatic cancer tissues and cell lines. They were miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b, miR-15b and miR-95 (70-73). Hence, it is beyond doubt these days that small molecules such as miRNAs have profound role in progression of pancreatic adenocarcinoma.

CONCLUSIVE REMARK:

The multilayer molecular pathology of pancreatic adenocarcinoma can only show us how complex the diseases could be and hence probably it can also reflect the challenges faced by the scientist to fight this kind of human malady. Although we can understand that, it is a mammoth task, but only by dissecting the molecular biology of such cancer is the only ray of hope.

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