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Epigenetics and Pancreatic Cancer: The Role of Nutrigenomics

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1. Introduction

Pancreatic ductal adenocarcinoma cancer is the 10th most commonly diagnosed cancer but is the 4th leading cause of cancer death in the United States. A number of risk factors have been proposed to play a role in the etiology of pancreatic cancer (1,2). Life-style factors such as smoking accounts for 20-30% of pancreatic cancer death, with approximately 10% having germline or somatic mutations association (3). Other risk factors include age, race, gender, chronic pancreatitis and diabetes; however, the role of dietary intake and specific nutrients remain an unexplored area of research, although diet is a risk factor (4,5). Epidemiological studies have long suggested the possibility that what we eat influence the state of our health. It is believed that dietary habits are important modifiable factors that can influence cancer risk and tumor behavior (6,7). *In vivo, in vitro* and epidemiological studies have shown that an individual's diet may contribute to their susceptibility to develop cancer (8-11).

Pancreatic cancer remains a very complex and challenging disease. This cancer carries one of the worst prognosis of any major malignancy, mainly due to its lack of early detection and lack of effective therapeutic agents. The American Cancer Society projected 43,140 new cases of the disease in 2010, and over 36,800 deaths (12). Improvements in imaging technology has aided in diagnosis and identification of patients with the disease; however, these new technologies have not greatly improved the mortality rate of pancreatic cancer. Clinical, pathological and genetics studies have identified three important different preneoplastic lesions of the pancreatic ductal adenocarinoma, the pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCM) which could be studied to identify early changes in pancreatic cancer (13,14). Understanding molecular changes within these preneoplastic lesion, whether genetic or epigenetic, will greatly improve detection of pancreatic cancer at its earliest stages. Furthermore, the examining of these lesions with emerging "omics' technologies and the emerging new science "nutriogenomics" will greatly contribute to our knowledge of this deadly cancer.

2. Nutrigenomics

Nutrigenomics is an emerging new field of science in which attempts are being made to study the effects of nutrition on the whole genome (15). Nutrigenomics is the study of

specific genes or the affect of functional single nucleotide polymorphisms and bioactive food components interactions. Although great emphasis has been placed on understanding the role of nutrigenomics on regulation of gene expression in regards to polymorphisms, very little data are available on the role of nutrigenomics and its role in epigenetic regulation. We must also include in this new area of science, high energy or caloric intake because of its contribution to obesity. Nutrients are thought to be dietary signals that can be detected by various cellular systems involved in regulating gene and protein expressions, as well as affecting the production of metabolites (16,17). Therefore, each individual can establish dietary signatures in specific cells, tissues or organs according to their daily diets, which could utlimately influence homeostasis and their susceptibility to diseases, such as cancer. Studying the effects of nutrients at the genomic level can be through genetic or epigenetic mechanisms. This chapter focuses on the role of epigenetic mechanisms in pancreatic cancer and their modulation through dietary agents found in daily food intake. The influence of bioactive components in foods on various biological and physiological functions at the genomic level is a vastly unexplored area of research in cancer research. Dietary components are beginning to be observed as major determinants of cancer risk in humans (18-22). Nutrition can potentially modify, through epigenetic mechanisms molecular changes associated with carcinogenesis. Furthermore, employing this new science in understanding how bioactive components can affect the constant insults from external and internal factors to DNA, which results in chromatin changes, alteration in DNA repair, apoptosis and inflammation epigenetically will enhance our knowledge on pancreatic cancer. This new field of science can begin to investigate the role of various nutrients on mechanisms that may influence the etiology or progression of pancreatic cancer.

3. Epigenetic mechanisms

Epigenetic modifications can be altered by external or internal environmental factors, such as diets, and has the potential to also be reversed (23,24). Epigenetic mechanisms include DNA methylation, histone modifications, and changes in microRNAs (25-28). These mechanisms can lead to changes in gene expression and have been the focus of a number of diseases including cancer, type 2 diseases, obesity, cardiovascular diseases, neurodegenerative diseases and immune diseases (29-33). Tumors can exhibit widespread global DNA hypomethylation, region-specific hypermethylation and increased activities of the DNA methyltransferases. DNA methylation modification is established and maintained by a family of DNA methyltransferases (DNMTs), DNMT1, DNMT3a and DNMT3b (34,35). These enzymes catalyze the transfer of methyl groups from S-adenosylmethionine (SAM) to cytosine residues in the DNA. These critical enzymes have been shown to be highly expressed in pancreatic cancer and play critical roles in silencing important genes, such as p16, RASSFIA, cyclin D2, APC and others through promoter hypermethylation in various cellular pathways (36-38). Approximately 60% of human genes are associated with CpG islands that are subject to methylation in tissue specific patterns; however, these islands have been shown to increase their methylation status during aging and the development of certain diseases such as cancer (39,40). Several of the classic tumor suppressor genes, such as p16/CDKN1A, p53, SMAD4 and STKll, have been genetically inactivated through DNA methylation in pancreatic cancer. hMLH1, which is associated with microsatellite instability, has been also shown to undergo methylation in pancreatic cancer (41,42). Several other genes with tumor suppressor properties have also been associated with pancreatic cancer (43).

Although much of the focus of cancer epigenetics is on inactivation of tumor suppressor genes by promoter methylation, the earliest observation of altered methylation patterns identified DNA hypomethylation as an important event in the etiology of cancer (44-46). Global DNA hypomethylation was first associated with the lack of critical nutrients such as methonine, folate, and vitamin B12 (47-49). These observations raised the importance of nutritional causes of methyl group deficiency and its association with the tumorigenesis. DNA hypomethylation is often associated with gene overexpression or gene activation. Nutrients deficiency can, therefore, influence the methylation status of an individual and increase their susceptibility to diseases such as pancreatic cancer. Given the role of the pancreas in digestion and absorption, diet may play a larger role in pancreatic disease and prevention.

In addition to DNA methylation, histone modification has also been implicated in pancreatic cancer, particularly genes of the mucin family (50-52). These genes have been found to undergo histone modifications in pancreatic cancers (53,54). Mucin gene products are high molecular weight glycoproteins that are produced by pancreatic cancers. MUC1, MUC2 and MUC3 histone modifications have been investigated and their role in pancreatic cancer is described in relation to nutrigenomics (55,56). MUC1 in normal pancreas is the main membrane-bound mucin expressed. MUC1 has been used as a marker of pancreatic ductal cells. MUCs are known to play important roles in protection and epithelial repair in the intestinal mucosal (57). MUC2 is absent or weakly expressed in ductal and acinar cells in normal pancreas. MUC2 has been shown to demonstrate tumor suppressor properties (58). However, in pancreatic cancer there is an altered expression pattern of mucins at different stages of pancreatic tumor progression (59). MUC1 gene expression is regulated by a combination of DNA methylation and histone H3-K9 modification (60).

4. Nutrigenomics and epigenetic regulation of signaling pathways

The past decades have focused mainly on research involving genetic alterations or genetic susceptibility due to germline mutations (61-64). Mutated KRAS has high mutation prevalence in pancreatic cancer, reaching as much as 100% in advanced stages of the disease (65,66). However, dietary agents such as high fat diets have been shown to increase KRAS expression (67-69), while other studies have shown decreased expression with caloric restriction (70,71) and intake of bioactive components found in some vegetables and fruits (72-75). Using global genomic screening, 12 altered core signaling pathways due to mutations have been found in pancreatic cancer (76). In addition to widespread genetic alterations, it is now apparent that epigenetic factors also play an important role in modulating a number of these signaling pathways in pancreatic cancer (77). Regulation of specific genes in a subset of regulatory pathways has been identified to be disrupted in pancreatic cancer and modulated by dietary agents (78). These pathways involve apoptosis, DNA damage control, K-ras signaling, JNK signalings, invasion, Hedgehog signaling, Wnt-Notch signaling, TGF-ß, and regulation of the G1/S phase transition (79-81). The dietary agent curumin, a yellow spice found in both turmeric and curry powder, inhibits JNK, COX2, NF-kappaB, STAT3 and AP-1 activation (82) through epigenetic mechanisms. The Wnt-Notch signaling pathway, which is altered in pancreatic cancer, control key biological processes that impact tumor progression and patient survival. Epigenetic inactivation of key components, such as the secreted frizzed-repeated protein (SERP1), in this pathway can lead to constitutively

activation of this pathway (83). EGCG, a component found in green tea extract, induces apoptosis and inhibits JNK signal pathway in pancreatic cancer (84,85). Inactivation of the human Runt-related transcription factor 3 (RUNX3), which play a role in TGF-ß signaling, decreases TGF-ß expression in pancreatic cancer (86). TGF-ß has been shown to be a potent inhibitor of pancreatic cancer cells *in vitro* (87). Recent data revealed the inactivation of the Hh-interaction protein (HHIP) through promoter hypermethylation in pancreatic cancer cells *in vitro*. HHIP is a negative regulator of the Hedgehog signaling pathway which is up-regulated in pancreatic cancer (88). The Hedgehog signaling pathway has been highly conserved through evolution and plays a crucial role during embryonic development (89). Dietary agents have been shown to modulate homologus of this pathway (90). In humans, there are three different homologues of the pathway, Sonic Hedgehog (Shh), Indian Hedgehog (IH) and the Desert Hedgehog (Dhh). Epigenetic mechanisms involve altered gene expression without changes in genomic sequences, thus these mechanisms can alter the above pathways through many factors, such as diet and life-style factors (e.g., smoking).

5. Dietary nutrients, obesity and caloric restriction

In the nutritional field, epigenetics is important because nutrients and bioactive food components can modify the expression of genes at the transcriptional level (91-93). There is a critical lack of research examining the role of critical nutrients on the etiology of cancers such as pancreatic cancer, although animals studies have indicated its role in cancer development for a number of years (94,95). However, to critically examine an individual's nutrients intake will require improvement over the current 24-hour recall survey often used in dietary studies.

Deficiency in proper nutrients, critical micronutrients and increase in high fat-diets or high caloric intake have been implicated in a number of diseases, including cancers, such as pancreatic cancer (96,97). The relationship between food, nutrition science and diseases such as cancer through epidemological studies have been analyzed for a number of years. However, the genomic variation among individuals and populations remains an unexplored area of research, which can enhance our knowledge in understanding complex diseases such as pancreatic cancer and its impact on the etiology and progression of this disease. The genomic era has ushered in a new science called "nutriogenomic" to began to understand the importance of nutrition on complex diseases such as pancreatic cancer, in which the disease presents little or no early symptoms for early detection or diagnosis. Obesity is a risk factor for pancreatic cancer in certain populations (98). Understanding these interactions will provide critical information for understanding how the health consequences of eating behaviors may vary across individuals or different ethnic groups. Although the survival rate of pancreatic cancer has slightly improved, African Americans continue to have the highest incidence rate of pancreatic cancer than any other ethnic groups (99). Eating behaviors and types of diets in this group as it relates to its effects on changes in the genome related to diseases such as cancer, remains an unexplored area of research. Bioactive components in foods can act on the human genome directly or indirectly to affect gene expression or their gene products. This new research area "nutrigenomics", in relation to pancreatic cancer, can ultimately identify molecular targets for nutritional intervention.

Numerous dietary components are known to alter epigenetic events, and thus can influence the health of individuals. Folic acid and vitamin B12 play an important role in DNA

metabolism and are required for the Synthesis of Methionine and S-adenosylmethionine (SAM), the common methyl donor required for the maintenance of DNA methylation patterns (100). Essential and non-essential nutrients or bioactive components have been shown to modulated and number of cellular processes through epigenetic mechanisms involved in carcinogen metabolism, cell signaling, cell cycle control, apoptosis, hormonal balance and angiogenesis (101).

Epidemiological evidence and the relation of nutrition and pancreatic cancer has been extensively reviewed (102). However, a number of these studies have included descriptive, case-control and often cohort studies, all showing a consistent pattern of positive association with nutrition and recently, research data showing correlation with increase pancreatic cancer and obesity (103). Some current studies have confirmed our early studies showing decreased rates of pancreatic cancer with caloric restriction (104). We reported this finding in the mid-90s and demonstrated that it occurred through DNA methylation, an epigenetic mechanism. Case-control studies have shown a correlation between caloric intake and higher risk of pancreatic cancer in African American and identified obesity as a risk factor for pancreatic cancer (105). Obesity during pregnancy and high-fat maternal diets have been shown to be associated with obesity in offsprings suggesting early imprinting (106). Studies are needed to address the specific nutrients or fats that may modulate gene expression through epigenetic mechanisms. Epigenetic biomarkers of obesity that have been identified include epigenetic regulation of genes involved in adipogenesis (SOCS1/SOCS3), methylation patterns of obesity-related genes (FGF2, PTEN, CDKN1A and ESR1), inflammation genes as well as genes involved in intermediary Metabolism and insulin signaling (107).

The degree of methylation can be determined by the availability of methyl donors, methyl transferase activity, and also demethylation activity. Studies have shown that chronic administration of methionine- and choline-deficients diets results in global hypomethylation of hepatic DNA and development of spontaneous tumor formation (108). In those studies when the pancreas was examined in the methionine- and choline-deficients diets, a transdifferentiated (hepatocyte-like) phenotype was observed (109). The progentic of these cells have now been identified as pancreatic stem cells (PSCs) that are capable of producing cells with multiple markers of other non-pancreatic organs (110). The fact that pancreatic cancer contains tumorigenic cancer stem cells and are highly resistant to chemotherapy and can be induced by a lack of micronutrients strongly suggest this area of research greatly needs exploring. Research using nutrigenomics can address the importance of tumorigenic cancer stem cells in pancreatic cancer.

6. DNA methylation and nutrigenomics

Bioactive food components have been shown to have benefical effects on the genome through epigenetic mechanisms. Certain bioactive components, such as tea polyphenols, genistein from soybeans, and isothiocyanates from plant food, may have inhibitory effect on certain cancer, including pancreatic cancer. Dietary polyphenols is thought to have a direct inhibition by interaction with the catalytic site of the DMNT1 or it could have an influence on the methylation status indirectly. A number of cultured cells, animal models and human clinical trials have shown the protective role of dietary polyphenols against a number of cancers, including pancreatic cancer (111). However, understanding the timing of

intervention is critical in cancer prevention, particularly for an aggressive cancer such as pancreatic cancer which lacks early biomarkers of detection. Epigenetic mechanisms are thought to play an early role in pancreatic cancer, such as inactivation of tumor suppression genes through hypermethylation of CpG islands in promoter regions of genes. Reversal of gene hypermethylation has been achieved by inhibiting DNMT activity in cancer cells. A number of studies are showing inhibition of DNMT activity with dietary components. We have shown reactivation of p16 in pancreatic cancer cells through DNA hypomethylation with the dietary agent indole-3-carbinol. Recently our laboratory has also shown that indole-3-carbinol can greatly enhance the efficacy of gemcitabine, which is the first line treatment for pancreatic cancer (112).

Epigallocatechin-3-gallate (EGCG) one the major components of green tea has been shown to be an effective DNMT1 inhibitor directly. Thus, activation of tumor suppression genes p16, RAR, MGMT and MLH1 have been demonstrated by EGCG. In addition, the protected effects associated with consumption of fruits and vegetables and various chemical components in pancreatic cancer have demonstrated various effects on pancreatic cancer cells, such as induction of apoptosis, inhibition of proliferation, inhibition of transcription factors, activation of suppressor genes and inhibiting K-ras signaling through epigenetic mechanisms (113). Modulation of these critical events by dietary factors through epigenetic changes is an important area of research that is needed in clinical trials with or without association with current chemotherapeutic agents. Table 1 shows a list of dietary factors know to regulate DNA methylation.

Bioactive Component
Coumestrol
Methionine
Genistein
Vitamin B12
EGCG
Indole-3-Carbinol
Vitamin B6
Folate
Equol
Choline
Curcumin

Table 1. Bioactive Components of Food that Influence DNA Methylation in Pancreatic Cancer

7. Histone modifications and nutrigenomics

Another epigenetic mechanisms that has been shown to be modulated by bioactive components in foods are histone modifications. Histones, which are the structural component of chromatin, are modified by methylation, acetylation, phosphorylation, biotinylation, ubiquitination, sumoylation, and ADP-ribosylation (114). Diverse histone modification is known to play an important role in gene regulation and tumorigenesis. The

modification involving epigenetic mechanisms occurs at the histone tails, that usually consist of about 15-38 amino acids. Majority of the modifications takes place at lysines, arginine and serine residues. These modifications can lead to either activation or repression depending on which resides are modified. Lysines residues in the tails can be either methylated or acetylated. Usually histone modification status is often balanced by a group of enzymes called histone acetyltransferases (HATs) and histone methyltransferases (HATs) which add acetyl and methyl groups; and histone deacetylases (HDACs) and histone demethylases (HDMs) which remove acetyl and methyl groups from histone protiens. Histone methylation is maintained by histone methyltransferases and histone demethylases. Histone acetylation results in an "open" chromatin structure thus allowing access to DNA and gene transcription. Acetylation of N-terminal lysine residues at positions 9,14,18, and 23 of H3 and 5, 8,12, of H4 mediates the decondensation of the chromatin for accessibility to transcription factors. Histone acetylation is one the most extensively studied histone modification. Deacetylation is often associated with silencing of gene expression. Dietary agents have been identified that have structural features similar to the HDAC inhibitors (115,116). HDAC inhibitors are known to reactivate epigenetically silenced genes.

Bioactive components have been found to act as HDAC inhibitors, such as butyrate, sulforophane, curcumin, resveratrol and diallyl disulphide. Butyrate, a short-chain fatty acid formed from the fermentation of fibre when consumed has been shown to downregulate transcription factors such as Sp1 and Sp2, which have been reported to be acetylated targets for HDAC1 and HDAC2 (117). This effect has been shown to increased p21 expression which will ultimately cause cell cycle arrest and an increase in Bax expression thus causing apoptosis. In pancreatic cancer cells sodium butyrate has been shown to sensitize these cells to Fas-mediated apoptosis as well as down regulation of Bcl-xL expression and apoptosis. Further research is needed to understand the role of dietary agents on histone modifications in pancreatic cancer. A number of studies have shown dietary agents such as curcumin, anacardic acid, garcinol, polyphenols, isothiocyanates, isoflavone and resveratrol to affect histone modifications. Resveratrol, a bioactive component of grape skins, exert its anti-inflammatory effect through repression of NF-κB induced by histone deacetylation (118).

Bioactive Component
Butyrate
Sulforophane
Curcumin
Resveratrol
Diallyl disulphide
Anarcardic acid
Garcinol
Polyphenols

Table 2. Bioactive Components of Food that Influence Histone Modification in Pancreatic Cancer

In addition to bioactive nutrients modulating histone modifications, studies have also shown that caloric restriction, another unexplored area of research on epigenetics, reduces the expression of inflammatory genes such as NF-κB, AP1, COX-2, and iNOS (119).

Reduction in total caloric intake has numerous health benefits, including reducing risk to certain cancers such as pancreatic cancer ( ).NF-κB is known to be activated by histone aceylation. Activation of NF-κB occurs through p300 HAT acetylation of the p50 subunit of NF-κB. This increases NF-κB binding and transactivation. Caloric restriction modulation of these pathways through epigenetics mechanisms allows numerous opportunities for prevention of diseases such as cancer.

8. microRNAs and nutrigenomics

In addition to DNA methylation and histone modification, another epigenetic mechanism, microRNAs is emerging as a key mediator in gene regulation which may be affected by bioactive dietary components. These small single-stranded RNAs, ~19-24 nucleotides in length, regulate gene expression through post-transcriptional silencing of targeted genes. MicroRNAs can play important roles in controlling both DNA methylation and histone modifications. This regulation creates a highly controlled feedback mechanism. In contrast, promoter methylation or histone acetylation can also modulate microRNA expression (120). Usually microRNAs can control a wide spectrum of biological function that may be relevant in cancer, such as cell proliferation, apoptosis, and differentiation. Aberrant expression of these small nucleotides have been associated with cancer. Several microRNAs have been identified that are regulated by DNA methylation in pancreatic cancers (121). Noncoding RNA and miRNAs are known to be involved in post-transcriptional gene silencing. Methyl-deficient diets and folate deficiency induce global increase in microRNA expression in some cancers.The relevance of microRNA and nutrigenomics is a greatly unexplored area of research as it relates to pancreatic cancer. However, curcumin has been linked to changes in microRNA expression in pancreatic cancer cell lines. Curcumin represses human pancreatic cancer cells by upregulating miR-22 and downregulating miR-199a. MicroRNA-10a expression, which has been identified as a mediator of metastatic in pancreatic cancer, is repressed by retinoic acid receptor antagonists (122,123).

Bioactive Component
Curumin
Polyphenols
Resveratrol

Table 3. Bioactive Components of Food that Influence microRNAs in Pancreatic Cancer

9. Conclusion

Finally, understanding the role of nutrigenomics on pancreatic cancer etiology through epigenetic mechanisms could have a tremendous impact on decreasing the mortality of this disease. The beneficial aspects of various nutritional bioactive components and their effects on inhibiting or decreasing pancreatic cancer could also enhance the efficacy of current therapeutics used in treating pancreatic cancer. Understanding the role of nutrigenomics and its impact on modulating epigenetic mechanisms such DNA methylation, histone modification and microRNAs in pancreatic cancer will greatly enhance intervention or prevention stagergy for this disease. Our knowledge in the field of this emerging science is currently very limited, but the potential is vast in understanding the role of various

nutrients on the genome and its ability to contribute to healthy life-style, thus decreasing individuals risk to diseases such as cancer. Although intake of some dietary components may not improve health, research in this field will identify the interaction of these components with various macromolecules in the cell that are not Benefical. The study of nutrigenomics could identify molecular targets for nutritional preemption and information obtained from these studies are key to personalized nutrition.

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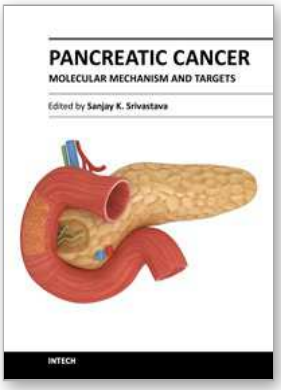

Pancreatic Cancer - Molecular Mechanism and Targets

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This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyante and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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