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Editorial

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Epigenetic Alterations in Pancreatic Cancer

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Pancreatic cancer is the fourth leading cause of cancer death and is predicted to be the second leading cause in a decade in the US. Despite more than 50 years of research and therapeutic development, pancreatic cancer still has a median survival rate of 6 months and a 5-year overall survival around 5%. Therefore, there is an urgent need to better understand the mechanism of pancreatic cancer development, as well as to discover new biomarkers for early diagnosis, prognosis, and therapeutic targets.

Recent whole genomic sequencing and copy number analysis of pancreatic ductal adenocarcinoma discovered many altered signaling pathways.[1-3] Most of the studies have been focused on genetic abnormalities of driver mutations that occur in more than 50% of the pancreatic cancer cases, such as KRAS, TP53, SMAD4, and CDKN2A. The other lower prevalence mutated genes include those involved in Deoxyribonucleic acid (DNA) damage repair, chromatin remodeling, WNT signaling, Transforming Growth Factor (TGF) beta signaling, Hedgehog (Hh) signaling, and cell cycle regulation pathways. Recently it also became evident that many genetic alterations in pancreatic cancer target epigenetic regulators.[4]

Epigenetics is the heritable alterations of gene expression without changing DNA sequence.[5] DNA methylation, histone modification (methylation, acetylation, phosphorylation, ubiquitination, and sumoylation), and non-coding Ribonucleic acids (RNAs) are the most important mechanisms of epigenetic regulations. These modifications alter chromatin structure and promoter accessibility, and thus lead to altered gene transcription. Recent studies showed that epigenetic alterations in cancer cells contribute to tumor initiation, progression, and metastasis. Whole genome sequencing studies revealed driver mutations in epigenetic regulators in human cancers. Some of the mutations are oncogenic (i.e. IDH1/2, EZH2, DNMT3A), and other mutations are tumor suppressive (i.e. KDM6A, CREBBP/EP300, SMARCB1).[5] Recent whole genomic sequencing in pancreatic cancer also revealed pathogenic mutations and structural variants in several epigenetic regulator genes including KDM6A, ARID1A, ARID1B, PBRM1, SMARCA2, SMARCA4, and MLL2.[1] Among those genes, KDM6A was inactivated in 18% of the pancreatic cancer patients. These findings further demonstrated that characterization of these epigenetic alterations will advance our understanding of the mechanisms contributing to pancreatic tumorigenesis, and lead to new discoveries of diagnostic and prognostic markers and therapeutic targets.

DNA methylation at gene promoter C-phosphate-G (CpG) island blocks transcription initiation, whereas methylation in gene body may facilitate transcription elongation and various splicing. DNA methylation is also frequently found in repeat-rich areas of the genome and is essential for chromosomal and genomic stability.[6] DNA methylation of tumor suppressor gene promoter is thought to be a major epigenetic mechanism in tumorigenesis. Gene promoters of Adenomatous Polyposis Coli (APC), Breast cancer 1 (BRCA1), and $p16^{INK4a}$ are among the most frequently methylated in human pancreatic neoplasms.[7] Aberrant gene methylation involves the genes in the TGF beta, WNT, integrin, SLIT-ROBO signaling, cell adhesion, and stellate cell activation pathways. DNA methylation is carried out by enzyme DNA methyltransferases (DNMTs). Interestingly, increased expression of DNMT1, DNMT3A and DNMT3B was reported in pancreatic cancer, suggesting their role in pancreatic cancer development. Mi-

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croRNAs (miRNAs) were also found to be misregulated in pancreatic cancer and its precursor lesions such as Intraductal Papillary Mucinous Neoplasm (IPMN).[8] Therefore, epigenetic alterations appear to contribute to pancreatic tumorigenesis.

Perhaps the most interesting epigenetic regulators in pancreatic cancer oncogenesis are the histone modification, especially histone methylation, and the chromatin remodeling complex SWItch/Sucrose Non-Fermentable (SWI/SNF). Most recent findings from the whole genomic sequencing data revealed that some of the most frequently mutated epigenetic genes in pancreatic cancer belong to these two families. Histone methylation occurs at the amino acid side chains of lysine, arginine, and histidine residues. Depending on which lysine residue is methylated, the result could be either transcription activation or silencing. Additionally, each residue can be mono-, di-, or tri-methylated, which provides another layer of regulation. In contrast, Lysine-specific demethylases (KDMs) remove the methyl group from histone. The two highly mutated histone methylation regulatory genes in pancreatic cancer are KDM6A and MLL2.[1] The ATP-dependent chromatin remodeling complexes are another group of important epigenetic alterations in pancreatic cancer with the SWI/SNF complexes being the most studied and mutated. ARID1A, ARID1B, PBRM1, SMARCA2, and SMARCA4 are all components of the SWI/SNF complexes, and were shown by genomic sequencing studies to be mutated in pancreatic cancer. The SWI/SNF complexes remodel chromatin through mobilization of nucleosomes both by sliding and by ejection/insertion of histone octomers.[9]

Due to the broad coverage of these epigenetic regulators across the genome, their genetic alterations have major impact on vital cellular processes such as differentiation and proliferation. Most of the mutations involving these epigenetic regulators are truncating mutations, either frame shift or nonsense mutations, although some are missense mutations.[10] It is most likely that these mutations are inactivating mutations. Some of the mutations were found in many types of human malignancies. Although most of the mutations occur in a relatively low frequency, it is believed that at least some of these mutations are driver mutations in cancer development. However, exactly how these mutations affect epigenetic reprogramming in different cell types and in different stages of tumor development is still not clear. Questions like whether these mutations have diagnostic, prognostic, or therapeutic value in pancreatic cancer patients and how they shape the gene expression profile are still waiting to be answered.

In summary, it has become clear that distinct epigenetic events are sufficient to drive tumor formation, progression, and metastasis. Recently, numerous mutations have been found in chromatin modifier genes. These mutations have been shown to have profound impact on tumor epigenetic regulation, leading to oncogenic transcriptional programs. New therapies are under development targeting epigenetic alterations (i.e. Isocitrate dehydrogenase (IDH1)). However, relative little is known about the implication of these epigenetic mutations in pancreatic cancer. There is no doubt that much needs to be done to better understand the mechanisms of epigenetic regulations in pancreatic cancer before translating these new discoveries into clinical practice.

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