# The Triple-Code Model for Pancreatic Cancer

## Cross Talk Among Genetics, Epigenetics, and Nuclear Structure

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**KEYWORDS**

• Pancreatic adenocarcinoma • Epigenetics • Triple-code hypothesis

**KEY POINTS**

- Many researchers and practitioners still see pancreatic cancer exclusively as a disease of epithelial exocrine cells, which become transformed by the accumulation of genetic alterations.
- Genetic alterations cross talk with epigenetic and nuclear structure changes to give rise to not only neoplastic transformation but also to determine most features of the cancer phenotype and its symptoms.
- This updated paradigm for the progression of pancreatic cancer integrates the concept that the patterns of gene expression networks to define the pancreatic cancer phenotype are dictated by the combination of genetic, epigenetic, and nuclear structure instructions according to the triple-code hypothesis, which considers that all of these codes contribute to the development and progression of this disease.
- Many epigenetic alterations are significantly ameliorated by a new type of therapeutics that targets the epigenome. Promising epigenetics-based therapies are currently being evaluated through different types of trials.

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Pancreatic adenocarcinoma (PDAC) remains a national health priority and significant therapeutic challenge. This dismal disease ranks fourth as a leading cause of cancer-related deaths in the United States, with a median survival of 6 months and a 5-year survival of 3% to 5%.[1] The bleak prognosis of PDAC is due to an aggressive biology, its immediate dissemination, and late diagnosis, rapidly leading to an incurable stage for which therapeutic intervention is a challenge. Surgical resection is the only curative modality; however, this only applies to 10% of patients, with their 5-year survival barely 20%.[2] Notably, these aggressive neoplasms are highly resistant to conventional chemotherapy and radiation.[3] Gemcitabine, a nucleoside analog, remains the standard chemotherapy option for metastatic PDAC.[4,5] Numerous trials have attempted to improve gemcitabine clinical benefit through alternative schedules or combination with other agents, to no avail.[6–8] Thus, there is an urgent need to develop novel therapies in PDAC, in particular, targeting pathways highly relevant to its pathobiology.

The genetics revolution has significantly advanced pancreatic cancer research. Searching for genetic mechanisms, many laboratories discovered oncogenes and tumor suppressor genes for PDAC.[9] These discoveries led to the seminal working model from the John Hopkins group[9] that expanded the understanding that PDAC arises from epithelial cells through accumulation of genetic alterations, driving transitions through increasingly aggressive lesions known as pancreatic intraepithelial neoplasias (PanINs). In particular, mutation of the *KRAS* oncogene is almost universally found in most PDAC cases.[10] Preneoplastic diseases, such as chronic pancreatitis, also harbor initiating *KRAS* mutations,[11] which seem to contribute to its evolution into cancer. This work prompted the development of animal models and tools to study, diagnose, and treat PDAC.[12,13] Thus, genetic concepts and tools have advanced the understanding of pancreatic diseases. Moreover, this work has led to the characterization of oncogenic signals that, for instance, in the case of kinases have allowed the development of novel therapeutics tools for this disease. However, despite these remarkable achievements, pancreatic cancer remains incurable.

The emergence of a new scientific revolution, epigenetics, has further advanced the study of pancreatic cancer by generating new tools for management and treatment. In 1942, Waddington[14] coined the term epigenetics to refer to inheritance that occurs independently of the coding capacity of DNA. Epigenetic mechanisms confer pluripotent progenitor cells that possess identical genomic DNA, the ability to differentiate into distinct populations. This wide range of differentiation originates from modulating genome expression in manners that are inheritable during cell division. Unlike genetics, epigenetics deals with the inheritance not of the genome but of the mechanisms that regulate the expression of entire gene networks at the right time, right time, level, and place to define and maintain the integrity of phenotypes. Since Waddington, it has been known that a cell has the potential to follow paths of distinct differentiation programs, similar to a ball rolling through different landscapes. Today, it is understood that these landscapes are defined by gene expression patterns. Recent Nobel Prize-winning discoveries have revealed that cells can be induced to undergo incredible phenotypic changes by manipulating gene expression in a manner that promotes rapid transit though these landscapes.[15] The generation of induced pluripotent stem cells, which promise to be key for cell-based therapies, involve the manipulation of the epigenetics of the cell, for example, in a manner that leads a fibroblast to convert into an adult pancreatic cell. More importantly, once they divide, these cells give rise to identical adult pancreatic cells. This fundamental stepping-stone will lead to the potential manipulation of the expressed genome for therapeutic purposes in a manner that will revolutionize biology and medicine. However, epigenetics promises much more. For instance, it is now known that, similar to genetic aberrations, epigenetic