ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2023 September 15; 15(9): 1505-1674

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 15 Number 9 September 15, 2023

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 9 September 15, 2023

Contents

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 9 September 15, 2023

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
September 15, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2023 September 15; 15(9): 1505-1519

DOI: 10.4251/wjgo.v15.i9.1505

ISSN 1948-5204 (online)

REVIEW

Deoxyribonucleic acid methylation driven aberrations in pancreatic cancer-related pathways

Akash Bararia, Amlan Das, Sangeeta Mitra, Sudeep Banerjee, Aniruddha Chatterjee, Nilabja Sikdar

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Niu ZS, China; Jin S, China

Received: April 18, 2023
Peer-review started: April 18, 2023
First decision: May 12, 2023
Revised: May 29, 2023
Accepted: August 1, 2023
Article in press: August 1, 2023
Published online: September 15, 2023

Akash Bararia, Nilabja Sikdar, Human Genetics Unit, Indian Statistical Institute, Kolkata 700108, India

Amlan Das, Department of Biochemistry, Royal Global University, Assam 781035, India

Sangeeta Mitra, Department of Biochemistry and Biophysics, University of Kalyani, West Bengal 741235, India

Sudeep Banerjee, Department of Gastrointestinal Surgery, Tata Medical Center, Kolkata 700160, India

Aniruddha Chatterjee, Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin 9054, New Zealand

Aniruddha Chatterjee, School of Health Sciences and Technology, University of Petroleum and Energy Studies, Dehradun 248007, India

Corresponding author: Nilabja Sikdar, PhD, Research Scientist, Doctor, Human Genetics Unit, Indian Statistical Institute, 203, B.T. Road, Kolkata 700108, India. snilabja@isical.ac.in

Abstract

Pancreatic cancer (PanCa) presents a catastrophic disease with poor overall survival at advanced stages, with immediate requirement of new and effective treatment options. Besides genetic mutations, epigenetic dysregulation of signaling pathway-associated enriched genes are considered as novel therapeutic target. Mechanisms beneath the deoxyribonucleic acid methylation and its utility in developing of epi-drugs in PanCa are under trails. Combinations of epigenetic medicines with conventional cytotoxic treatments or targeted therapy are promising options to improving the dismal response and survival rate of PanCa patients. Recent studies have identified potentially valid pathways that support the prediction that future PanCa clinical trials will include vigorous testing of epigenomic therapies. Epigenetics thus promises to generate a significant amount of new knowledge of biological and medical importance. Our review could identify various components of epigenetic mechanisms known to be involved in the initiation and development of pancreatic ductal adenocarcinoma and related precancerous lesions, and novel pharmacological strategies that target these components could potentially lead to breakthroughs. We aim to highlight the possibilities that exist and the potential therapeutic interventions.

Key Words: Methylation driven pathways; Pancreatic cancer methylation markers; Signaling pathway targeted therapy; PanCa enriched methylated pathway; Pre-cancer methylated pathways

Core Tip: Given the limited commercial availability of targeted epi-drugs and pathway-based biomarkers, it is important to generalize them for appropriate treatment of pancreatic cancer and related precancerous lesions. We also highlighted the clinical use of these therapeutic targets based on methylation driven pathways. This review will successfully help readers address current issues and support cutting-edge development of targeted therapies using epigenetically regulated pathways.

Citation: Bararia A, Das A, Mitra S, Banerjee S, Chatterjee A, Sikdar N. Deoxyribonucleic acid methylation driven aberrations in pancreatic cancer-related pathways. *World J Gastrointest Oncol* 2023; 15(9): 1505-1519
URL: https://www.wjgnet.com/1948-5204/full/v15/i9/1505.htm
DOI: https://dx.doi.org/10.4251/wjgo.v15.i9.1505

INTRODUCTION

Pancreatic cancer (PanCa) is one of the fatal malicious carcinomas globally. Currently, PanCa is one of the foremost causes of death by cancer especially in the United States[1]. According to GLOBACON 2020, PanCa is the 12th most common cause of cancer with 495000 new cases worldwide, of which approximately 47% of new cases occurred in Asia and another significant proportion, 28%, in Europe[2]. By the end of 2022, the incidence could increase by 70%, equivalent to about 844000 new cases per year[3]. Recent studies elucidate deoxyribonucleic acid (DNA) methylation depiction from inflammatory diseases thus opening a new profile for the biomarker development in early prognosis. Cell-free DNA methylation, in particular, could be used to identify pre-neoplastic features in individuals with suspected pancreatic disorders. This is a clear non-invasive approach of PanCa pre-diagnosis[4]. It is observed through the years that PanCa consists of extremely fatal malignancies, having less than 5 year of survival rate. Early detection and treatment of this disease is hampered due to a lack of reliable diagnostic and prognostic markers[3]. It has been noted that there is epigenetic variance between populations which can be accounted for by a variety of racial, demographic, and vocational characteristics. Only a few research have examined the Pancreatic ductal Adenocarcinoma (PDAC) progression stage globally and the shifting epigenetic landscape in various ethnic groups[5]. Recent research has demonstrated the dynamic changes in the global DNA methylation and gene expression patterns play important roles in cancer development, including PanCa development. These findings offer important new information for understanding the onset and progression of this malignancy[5].

PanCa is clinically allied with an elevated rate of mortality. In terms of geographic features, Northern America and Europe show the maximum prevalence of PanCa where more males tend to get affected. There are an estimated 62210 (male) and 32970 (female) new cases in the United States alone in 2022, with an estimated 25970 male and 23860 PanCa-related deaths[2,3]. In South Eastern countries like India, the rate of incidence of PanCa are comparatively lower compared to the Western world. According to per year statistics in Eastern countries like in India, the rate of prevalence of PanCa seems to be 0.5 to 2.4 out of 100000 women and 0.2 to 1.8 out of 100000 men. Although, regardless of the prevalence of this deadly disease, patient survivability with PanCa is comparatively downcast with 1 to 5-year of relative survival rates for all stages[6]. The main reason for such miserable and prolonged consequences is perhaps because of the fact that this fatal disease is predominantly lacks any symptoms in the early stages. Meanwhile, the symptoms commence to expand largely and eventually tend to get metastatic in nature[7]. As a result, enucleating a metastatic tumor is frequently impossible. PanCa has a 1-year survival rate of 26%, and the 5-year survival rate is roughly 6% for advanced cancer and 22% for early stages when surgical removal of the tumor is still possible[8]. For this reason, few new therapeutic strategies like radiotherapy and chemotherapy are effective to mitigate the tumor size in selected PanCa patients[9]. Hypermethylation in DNA methylation can promote tumorigenesis. However, with histone and RNA methylation, both writers and erasers can be PanCa oncogenes such as *SMYD3, KDM1, MELLT3* and *FTO*[10].

The study of malignant genomic modifications has been ongoing over the past few decades, and it has become quite evident that epigenetics are crucial to carcinogenesis. DNA methylation, a key component of epigenetics, affects a variety of biological functions, including gene imprinting, genome stability, and cell differentiation. Hypermethylation and hypomethylation are the two categories of abnormal DNA methylation. DNA hypomethylation refers to less DNA methylation, which frequently causes disturbance of chromosome stability or increased aneuploidy. On the other hand, DNA hypermethylation refers to the buildup of methylation, which mostly results in transcriptional repression and reduced gene expression. Typically, abnormal DNA methylation can be seen in the promoter regions of transcription factors, which promotes the growth and metastasis of cancers[11,12]. DNA methylation plays a crucial role in the onset and progression of cancer. Early on in the tumorigenic process, DNA methylation alterations frequently take place. This phenomenon has been confirmed for the bladder, lung, breast, colorectal, and pancreatic pre-neoplastic lesions[13,14].

According to Thompson *et al*[15], 2015, out of around 250000 assessed CpG sites, 20000 hotspots were correlated with patient survival. The two categories that were survival (-) and survival (+) which represented the connection between higher methylation and survival. The survival (+) sites were more evenly dispersed intragenically, whereas the survival (-) sites tended to group close to the TSS (transcription start site), indicating hypermethylation of promoter regions. An increased methylation pattern, associated with shorter survival was observed in survival (-) groups, while reduced methylation led to longer survival times in survival (+) groups. Some of the important genes [within the top 10 in survival (-) groups] which were found to be hypermethylated were *FAM150A, ONECUT1, RASSF10, RNF207,* PanCa DH9. The tumor-suppressor role of these genes are well-established in other aggressive cancers. While the genes such as *PTPRN2, MAD1L1, CBFA2T3, COL5A1,* and *SHANK2* etc. made their way into the top ten differentially methylated genes in the survival (+) group[16]. Thus, this segmentation, together with the fact that promoter regions of genes are typically better defined and documented, led to the surviving sites producing a clearer recovery of functional annotation and genes overall[17]. There is growing evidence that DNA methylation can affect how genes are expressed, despite the fact that the majority of research on DNA methylation has focused on the methylation state of promoters and CpG islands. Importantly, a mutation of *KRAS* in acinar or ductal cells causes the development of pancreatic lesions, which is the causative genetic event in over 90% of PDAC cases (PanIN). Along with the *KRAS* mutation, subsequent deletion mutations or mutations of other types in tumor suppressor genes promote tumor growth and accelerate the course of the disease[10,18].

The Advantageous incidence of this systematic review is to summarize all the differential methylation pathways in several precancerous lesions of PanCa. The alterations in epigenetics occurring in PanCa also discussed in this review. This review also gives insight into landscapes of the early epigenetics in precursor lesions. In this review also highlighted the differentially methylated enriched signaling pathways and methylated modulators, and their therapeutic targets for precancerous as well as PanCa. In brief, we describe an overview of differentially methylated genes, highlighting their diagnostic or prognostic potential in PanCa related enriched pathways (Figure 1).

PRECANCEROUS LESIONS OF THE PANCREAS

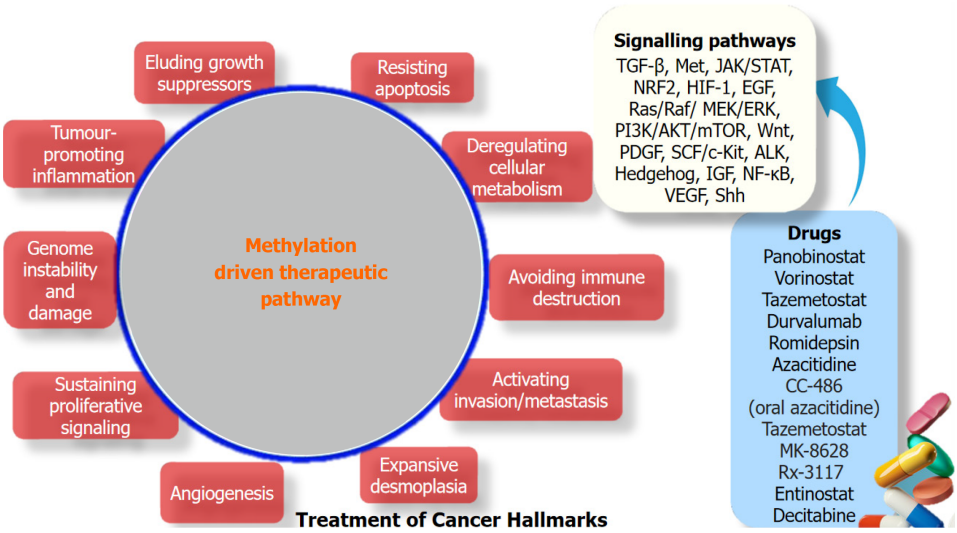
PanCa shows a proclivity for almost about 5 to 7 years of retention rate. Over the years it has been observed that a significant number of patients execute an immensely impoverished prophecy. Recent clinical studies clearly depict that throughout a long period of time; over 10 to 11 years, cellular level observation shows a clear tendency to originate various invasive proficiency. These series of phenomena conciliate the detection factors as well as root out the precursor lesions in PanCa[19]. From recent clinical studies, it is observed that the prior detection of these precancerous lesions put forward the possibility to reduce the death rate. The studies also delineate the fact that several non-intrusive prototype lesions exhibit malignant PanCa. From the surgical history of PanCa, it has been observed that patients having a previous history of PDAC may have microscopic pancreatic intraepithelial neoplasms (PanINs). Furthermore, these multifocal PanINs is clinically allied with diagnosable lobulocentric atrophy. Moreover, Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCN) are another couple of prominent pre-cancerous lesions which give rise to PanCa. These lesions are often considered to form cysts as well[20]. The surgical treatment and revelation of these MCN, IPMNs and PanINs can often create disturbance in the advancement to incursive PanCa. These eventually shows a high efficacy to save the lives of cancer patients[3,20].

PANCREATIC CANCER AND ITS EPIGENETICS LANDSCAPE

Due to epigenetic alterations, oncogenic signaling pathways specifically derived from transcriptional deregulation create a trademark to PanCa. 5-Hydroxymethylcytosine (5-hmC) is a chemical (epigenetic) modification of DNA at regulatory regions that result in the generation of 5-methylcytosine (5-mC) residue and has been thoroughly studied in PanCa. Genome analysis of 5-hmC occupied loci was done in the cell lines of short-passaged PanCa. As a result, surprising patterns of alteration were seen in neoplastic tissues in primary cancer patients[19,21]. It was observed that near the open chromatin regions, the 5-hmC was very much enhanced and thus tends to show upregulation of the allied transliteration [22]. The transcripts involve a few important oncogenic signaling pathways enmeshed in pancreatic neoplasia, such as *KRAS,* master regulator of cell cycle (*MYC), BRD4* and *VEGFA* where *BRD4* tends to be highly overexpressed in nature. In terms of functional approach, accession of 5-hmC at promoter *BRD4* was implicated along with the transcript expression elevation specifically in primary patient samples. It was also noticed that the in *in-vivo* experiments the growth of PanCa is highly inhibited by the *BRD4* blockage. Concisely, it can be said that in human PanCa and oncogenic enhancers, partisan enhancement and 5-hmC reallocation tend to be an important regulatory mechanism[22,23].

ROLE OF THE KEY PATHWAY MODULATORS IN PANCA AND ITS ASSOCIATED PRECANCEROUS LESSIONS

In PanCa, some important pathways are Raf/Ras/ERK. MEK interposes specific cellular responses to a few growth factor actions. In the past years, inhibitors emergence is highly noticed that directly target *KRAS*. This circumvents the long-harboured speculation that drugs cannot be produced by *KRAS*. In PDAC, several attempts have been made to target this



DOI: 10.4251/wjgo.v15.i9.1505

Figure 1 Comprehensive visualization showcasing interaction between epigenetic pathways and probable drug treatments concerning pancreatic cancer. EGF: Epidermal growth factor; Ras/Raf/MEK/ERK: Rat sarcoma virus/Rapidly Accelerated Fibrosarcoma/Mitogen-activated protein kinase/extracellular-signal-regulated kinase; PI3K/AKT/mTOR: Phosphoinositide 3-kinases/Ak strain transforming/Mammalian target of rapamycin; Wnt: Wingless-related integration site; PDGF: Platelet-derived growth factor; SCF/c-Kit: Stem cell factor/receptor tyrosine kinase; ALK: Anaplastic lymphoma kinase; TGF-β: Transforming growth factor beta; HGF: Hepatocyte growth factor; JAK/STAT: Janus kinase/signal transducers and activators of transcription; BTK: Bruton tyrosine kinase; Src: Tyrosine-protein kinase (sarcoma); COX-2: Cyclooxygenase 2; NRF2: Nuclear factor erythroid 2–related factor 2; HIF-1: Hypoxia-inducible factor-1; PKCδ-PKD1: Protein Kinase Cδ-Polycystin 1, Transient Receptor Potential Channel Interacting; IGF: Insulin like growth factor; VEGF: Vascular endothelial growth factor.

important oncogenic pathway in various approaches. The downstream regulation of frequently mutated *KRAS* is eventually considered to be an esoteric drug target[24,25]. On the other hand, owing to the offsetting mechanism that involves the enzyme, geranylgeranyl transferase, the upstream regulation of *KRAS,* using inhibitors like farnesyltransferase has been completely nugatory[26]. It is also observed that the inhibitors like *MRTX8, AMG510* and others specifically target only the *KRAS* mutant variant such as G12C[27,28]. Over 1%–5% of PDACs portray this kind of mutation and the progress is really promising. In PDAC, to regulate the antitumor pursuit in *KRAS*, the genetic inhibition of some autophagy regulators reciprocally enhances the propensity of *ERK* inhibitors (Table 1)[29].

EPIDERMAL GROWTH FACTOR PATHWAY MODULATORS

Epidermal growth factor receptor (EGFR) functions in a significant way in PanCa specifically in terms of tumorigenesis. Epidermal growth factor (EGF) is one of the classic pathways that works in a dysregulated manner in PDAC and is thus often considered as a potent therapeutic target. EGF signaling pathway inhibitors are considered as one of the efficient and significant regulators for cellular viability. These pathway regulators often mediate a wide range of signaling activities, precisely Jak-STAT, Akt/PI3K, Ras/Raf/ and MEK/ERK[29,30]. In PanCa patients, it is often noticed that affirmative activation and regulation of *EGFR* works effectively for the activation of *KRAS* and *ERK* and this persuades the formation of tumor more profoundly[31]. It is found that in Phase III clinical trial, the add-on of erlotinib elevates more positive improvements in cell survival in PanCa patients. The presence of *KRAS* gene (wild type) in PDAC tumors with a tiny proportion also leads to a significant improvement in PDAC patient survival[27,31].

WNT PATHWAY MODULATORS

In case of tissue development and maintenance in both embryos and adults, The Wnt signaling pathway plays a critical role. Digressive activation of this Wnt pathway has been closely associated with cancers like PanCa, specifically to the severely affected digestive tract. It is observed that Cancer stem cells are strongly associated with the activation of this pathway[32]. Furthermore, a precise monoclonal antibody named Wnt inhibitor vantictumab, which eventually targets the decrepitate receptor. This depicts a huge responsive activity of tumors and is often found to be combined with gemcitabine[33].

Table 1 Targeting various characteristics of pancreatic carcinomas and their associated therapeutic strategies

Potent therapeutics	Cancer Hallmarks
TGF-β pathway inhibitors HGF; Met pathway inhibitors	Activating invasion/metastasis
JAK/STAT pathway inhibitors; BTK inhibitors; Src inhibitors; COX-2 inhibitors	Tumour-promoting inflammation
NRF2 pathway inhibitors; HIF-1 pathway inhibitors; PKCδ-PKD1 inhibitors; Amino acid transporter inhibitors; α-Glucosidase inhibitors	Deregulating cellular metabolism
EGF pathway inhibitors; Ras/Raf/ MEK/ERK pathway inhibitors; PI3K/AKT/mTOR pathway inhibitors; Wnt pathway inhibitors; PDGF pathway inhibitors; SCF/c-Kit pathway inhibitors; ALK pathway inhibitors; Hedgehog pathway inhibitors	Sustaining proliferative signalling
IGF pathway inhibitors; NF-κB pathway inhibitors	Resisting apoptosis
VEGF pathway inhibitors	Inducing angiogenesis
Shh pathway inhibitors; FAK inhibitors; Src inhibitors; EGFR inhibitors	Expansive desmoplasia
Aurora kinase inhibitors; Cyclin-dependent kinase inhibitors	Eluding growth suppressors
PD-L1 inhibitors; CTLA-4 inhibitors	Avoiding immune destruction
PARP inhibitors Photodynamic agents; Bromodomain inhibitors; HDAC inhibitors	Genome instability and damage

EGF: Epidermal growth factor; Ras/Raf/MEK/ERK: Rat sarcoma virus/Rapidly Accelerated Fibrosarcoma/Mitogen-activated protein kinase/extracellular-signal-regulated kinase; PI3K/AKT/mTOR: Phosphoinositide 3-kinases/Ak strain transforming/Mammalian target of rapamycin; Wnt: Wingless-related integration site; PDGF: Platelet-derived growth factor; SCF/c-Kit: Stem cell factor/receptor tyrosine kinase; ALK: Anaplastic lymphoma kinase; TGF-β: Transforming growth factor beta; HGF: Hepatocyte growth factor; JAK/STAT: Janus kinase/signal transducers and activators of transcription; BTK: Bruton tyrosine kinase; Src: Tyrosine-protein kinase (sarcoma); COX-2: Cyclooxygenase 2; NRF2: Nuclear factor erythroid 2–related factor 2; HIF-1: Hypoxia-inducible factor-1; PKCδ-PKD1: Protein Kinase Cδ-Polycystin 1, Transient Receptor Potential Channel Interacting; IGF: Insulin like growth factor; VEGF: Vascular endothelial growth factor.

STEM CELL FACTOR/C-KIT PATHWAY MODULATORS

In several cell lines of PanCa, the occupancy of c-Kit has been clearly mentioned. The stem cell factor tends to reinforce the differentiation as well as the proliferation of cells and also seems to be expressing towards its ligands. Masitinib tends to strongly inhibit both the platelet derived growth factor and stem cell factor signaling pathways, thus delivering such extremely promising outcomes. This affirmative feedback is often found to be combined with gemcitabine[34]. Moreover, this c-Kit pathway inhibitors effluxes the overexpressed *ACOX1* marker which elucidates the efficiency in cancer patients [35].

PI3K/AKT/MTOR PATHWAY MODULATORS

The inhibitors of some specific signaling pathways like PI3K/mTOR and Akt bring into play some indispensable control over multifarious processes that are closely related to the growth and survival of cells in case of disease as well as health [36]. The mTOR/Akt and PI3 pathways also play distinctive key roles in several important cellular mechanisms like cell invasion, adhesion, and migration[37].

ROLE OF EPIGENETIC MODULATED PATHWAYS IN PANCA

Whole genome and exome sequencing has shown that a considerable portion of PDAC patients also carries non-germline mutations in chromatin remodelling complexes and epigenetic regulators, such as *ARID1A/B, MLL2/3/4, PBRM1, SMARCA2/4,* and *KDM6A* in addition to germline mutations. Moreover, the inactivation of *KDM6A, MLL3,* and *MLL5* (histone modification enzymes) and non-germline mutations in *ARID1A* occurred simultaneously with oncogenic *KRAS* in insertional mutagenesis screening of sleeping beauty transposon[38]. Vincent *et al*[39] discovered that the histone-modifying enzyme-coding genes were mutated in all of the malignancies in our screen. These mutations helped oncogenic *KRAS* accelerate the progression of PDAC, indicating that changes to the epigenome are crucial for accelerating PDAC. These results demonstrate the importance of epigenetic regulation in the progression of PanCa[40].

Transcriptional silencing is linked to abberant CpG island methylation of multiple tumor suppressor genes, including p16, in pancreatic and other carcinomas. In 15% of PanCa, the p16 gene is reported to be inactive due to hypermethylation of the CpG island. With higher PanIN grades, there is a greater tendency for the loss of p16 protein production, The *ppENK* gene exhibits anomalous methylations in pancreatic carcinomas, as was recently established using representational difference analysis and methylation CpG island amplification (MCA)[41].

PENK DNA methylation has been widely observed in precancerous lesions of varying severity, including extra- and intraluminal PTs and CPs, PanINs, IPMNs, and mucinous cystic neoplasms. Changes in PENK methylation increased with increasing coverage of tumor tissue, but were absent in autoimmune pancreatitis (AIP) and adjacent normal pancreatic tissue[3].

The m6A demethylase *ALKBH5* was found to be downregulated in a gemcitabine-treated patient-derived xenograft model, and its overexpression made PDAC cells more sensitive to treatment. Reduced *ALKBH5* levels predict poor clinical outcome in PDAC and other malignancies. Furthermore, both *in vitro* and *in vivo,* downregulation of *ALKBH5* greatly promotes PDAC cell proliferation, migration, and invasion, whereas overexpression has the opposite impact. The m6A global profile indicated changes in the expression of certain *ALKBH5* target genes, such as Wnt inhibitor 1 (WIF-1), which associated with Wnt signaling pathway mediation and WIF-1 transactivation[42].

Met-enkephalin, a tonically active inhibitory factor that interacts with the opioid growth factor receptor, is encoded by the *ppENK* gene. Met-enkephalin was found to slow the growth of various human cancers, including PanCa, according to Zagon and colleagues. Comb and associates claim that the CpG island methylation of *ppENK* directly prevented a positively active transcription factor from binding, which in turn suppressed the production of the gene. Given this, it is a possible outcome that cell growth and carcinogenesis of the pancreas are promoted because of the methylation of the ppEK gene[41]. Moreover, α-catenin, angiogenesis inhibitor *BAI3, CTNNA2, DPP6* (dipeptidyl-peptidase), *GUCY1A2* (guanylate cyclase), heterotrimeric G-protein-coupled receptor, protein kinases like *PRKCG,* and *Q9H5F0*- these genes were often altered at significantly lower frequencies[43]. According to the reports of Li *et al*[44] a total of 16420 genes having methylation information were found to be differently methylated, including 40 and 831 significantly hypomethylated and hypermethylated genes, respectively. *SARM1, IRX4, IRF4, FOXC2, EN2, ZSCAN23, PTPN5, HOXB4, CACNA1,* and *IGF2BP1* were the 10 genes with the most significantly different methylation patterns. The 10 genes with the most different methylation patterns were *REG4, C11orf34, BRD9, S100A16, HIST1H2BK, STATH, LRRC31, UBD, MIR548A1,* and *PSMG3*[45].

Processes like the differentiation of neurons in the CNS, neuropeptide signaling pathway and organ development at the embryonic stage, were the most observed enrichment functions. According to the study, these genes were primarily engaged in signaling pathways for neuroactive ligand-receptor interaction, cAMP, salivary secretions, glutamatergic synapses, calcium, morphine addiction, circadian rhythm, nicotine addiction, and pancreatic secretions. Genes that significantly affect survival were included as taxonomic features in order to define molecular subtypes of PDAC in relation to prognosis[46]. An important finding from the univariate Cox proportional hazards regression model developed for clinical factors indicated that age should be considered as a significant parameter related to patient survival. These 135 significantly differentially methylation genes were included in the above-mentioned multivariate regression model together with age as a covariate to find variables that independently influence prognosis. Using multivariate Cox regression models, 78 differentially methylation genes substantially linked with prognosis were discovered[46,47].

Chatterjee *et al*[5], identified "regulation of ion transport", "alpha/beta interferon signaling", "morphogenesis and development" and "transcriptional dysregulation" as the four most statistically significant extended terms. Voltage-gated ion channels are membrane proteins that selectively transport ions and are activated by changes in membrane potential. The activation of channels permits potassium ions to move along the electrochemical gradient. Hypermethylation of the *KCNA3* gene promoter may explain the poor expression of Kv1.3 in PDAC. The modulation of ion channels has been demonstrated to play a significant role in the regulation of cell death, evasion, and survival in the context of PDAC invasion and development.

In a study by Nones *et al*[48] 25 pathways were reported to be significantly affected by DNA methylation in PDACs. Axon guidance was one of the most significant (adjusted *P* value 5 1.91E-05) and was supported by MetaCore pathway analysis. This pathway was recently implicated in PDAC. Other pathways identified here as enriched for genes aberrantly methylated including cell adhesion, hedgehog signaling, TGF-b, integrin signaling and WNT/NOTCH signaling are well-known key cancer signaling previously described to be genetically altered in PDAC. WNT signaling has been reported to be aberrant methylated in PDAC cell lines. Our results confirm that this pathway is aberrantly methylated in this large cohort of PDAC. Stellate cell activation (adjusted *P* value3.26E-05) another interesting pathway identified here as significantly affected by DNA methylation deserves further investigation due its importance in PDAC. Pancreatic stellate cells are the main fibroblastic cells in PDAC and are known to interact with PanCa cells creating the fibrotic microenvironment of PDAC. It is hypothesized that the fibrous microenvironment of PDAC creates a barrier that impairs the delivery of chemotherapeutic drugs and promotes aggressive behaviour of tumor cells. Known genes are involved in astrocyte activation [cyclooxygenase-2, transforming growth factor-beta receptor 1, EGFR, tumor necrosis factor-alpha and MET were hypomethylated in PDAC and confirmed by bisulfite amplicon deep sequencing[48].

miRNAs are frequently suppressed in cancer cells and have the potential to act as tumor suppressors. Several miRNAs have been implicated in the development and spread of cancer in the pancreas, and it may one day be possible to stop the disease's progression by increasing the activity of a particular miRNA within a cell. The Food and Drug Administration (FDA) -approved drug Miravirsen, which employs miRNA to treat hepatitis C, has sparked interest in miRNA-based medicines for the treatment of PanCa. Regrettably, no treatments employing miRNAs or siRNAs that are comparable to them have been tried in clinical trials to treat PanCa, therefore miRNA will not be explored in great detail in this review. Nevertheless, we recommend individual study into the state of the art in miRNA studies[49].

In addition to confirming the mutations in the tumor suppressor and classical PDAC-associated oncogenes listed above, sequencing efforts have also revealed mutations in a variety of chromatin-modifying enzymes and complexes. The chromatin remodelers like, SWI/SNF family which alters nucleosome structure using ATP and accessibility of DNA in order to control gene transcription, includes the *ARID1A* component as one of their most often altered genes. 6% of the *ARID1A* mutations in human PDAC were found using multiplatform sequencing analysis. Although the role of *ARID1A*

as a PDAC-associated tumor suppressor gene is well documented, lymph node or distant metastases do not coincide with its expression levels. Instead, they are related to tumor stage and differentiation. When *ARID1A* is knocked out, acinar to ductal metaplasia and PanIN lesions develop as a result[41]. It's interesting to note that a recent study using genetically altered PanCa mice models demonstrated the importance of the survival gene Arid1a, whose absence inhibits cell development and causes cell death. In Ras-driven animal models, the deletion of *ARID1A* also prevents cell growth, leading to the emergence of inactive and low-quality cystic precursor lesions known as IPMNs[50]. The progression of Arid1a-deficient progenitor cells to adenocarcinomas, however, occurs during carcinogenesis *via* routes involving *Tp53* loss or Myc overexpression. PDAC has also been linked to mutations in the SWI/SNF subunits *SMARCB1, ARID1B, BRG1, PBRM1, SMARCA2,* and *SMARCA4.* In PanCa cell lines, *BRG1* inactivating mutations and deletions have been discovered. *BRG1,* a crucial entity of the SWI/SNF chromatin remodelling complex, is an ATP-dependent helicase. Neoplastic lesions that mirror human intraductal papillary mucinous neoplasms are produced as a result of *BRG1* deletion and *KRAS* mutation, which aids in the progression of PDAC[41,51].

Methylation at particular genomic locations may put patients at risk for tumor recurrence following total surgical removal and may be a sign of local and/or systemic metastasis. The surgical resection margin methylation profile may be used as a biologic marker in the absence of histologic disease to detect remaining pancreatic tissue that is susceptible to tumor recurrence or that harbours multi-focal disease throughout the gland. The link between methylation abnormalities and Auto immuno pancreatitis (AIP), a representative Immunoglobulin G4 (IgG4)-related illness, has yet to be determined. Through methylation array research using the Methylation 450K BeadChip array, the scientists discovered that sphingosine kinase inhibitor (SKI) may have a major methylation anomaly in AIP and explored the connection of SKI with AIP clinicopathological characteristics. AIP had a considerably lower SKI methylation ratio than PDAC and nurse practitioner (NP). Furthermore, the immunohistochemical staining-index (SI) score for SKI in AIP was substantially greater than in NP, despite no significant difference between AIP and PDAC[52]. Both the serum IgG4 concentration and the SKI methylation ratio showed a strong negative connection between the SI score and the methylation ratio. SI and the serum IgG4 concentration were shown to be somewhat positively correlated. Givien that SKI is regarded as an oncogene, hypomethylation of SKI and carcinogenesis may be connected to AIP[53]. Additionally, the association between serum IgG4 levels and SKI methylation raises the possibility that SKI plays the role in the aetiology of AIP. *NPTX2*, along with Cyclin D2, *FOXE1, TFPI2, ppENK,* and p16 all had hypermethylation events (10%) according to a research by Kinugawa *et al*[54]. However, compared to NCA and NP, AIP had a considerably greater*TFPI2* methylation ratio.

THERAPEUTIC ASPECTS OF EPIGENETIC MODULATED PATHWAYS IN PDAC AND ITS ASSOCIATED PRECANCEROUS LESIONS

PDAC is a deadly illness with few therapy options. According to new research, PDAC includes numerous layers of epigenetic alterations. Because the change is possibly reversible, it is a possible therapeutic target. Epigenetic changes can potentially affect the tumor microenvironment, modulating and enhancing treatment. Because epigenetic changes occur early in the disease, epigenetic markers can also be employed as diagnostic screening tools. Immunotherapy is being used more frequently to treat solid organ tumors, however there is no benefit for PDAC because most patients do not respond to these new treatments[55,56]. Because epigenetic processes regulate underlying immune cell activities, resulting in an anti-tumor response, combining immunotherapy and epigenetic therapy may improve patient outcomes even more. PDACs are currently classified as three to five subtypes according on the system used[57,58]. Using transcriptomic profiling, two primary molecular subtypes of PDAC were discovered: classical and basal[59]. The traditional kind has a better prognosis and clinical significance. Basal subtypes have altered the methylation of effectors and inhibitors of the Wnt signaling pathway by analyzing the epigenomic landscape. Classical tumors are hypomethylated, resulting in upregulation of the cholesterol transporter *NCP1L1*[60]. Furthermore, basal tumors were discovered to contain dysregulation of multiple genes related with established oncogenic signaling networks, including the *MYC*, erythroblastic oncogene B/*EGFR*, and transforming growth factor *(TGF)* signaling pathways. Chronic pancreatitis is a well-known risk factor for PDAC, which is consistent with the previously documented general link between tumor and inflammation[61, 62]. Early stage PanCa caused by inflammation is linked to epigenetic alterations. Damage to the pancreatic epithelium during a pancreatitis episode results in long-lasting transcriptional and epigenetic remodelling that creates epithelial memory that protects against strokes in the future[63].

Reader proteins, have lately been identified as prospective therapeutic targets, in particular the chromatin adaptors of the bromo and extra C-terminal (BET) family, after directly engaging with the histone tails with acetylated lysine residues, these proteins with bromodomains can bind transcription factors to the DNA, boosting the acetylation-induced transcriptional activation. BET proteins use the epigenetic landscape in this way to support the growth of PDAC cells. Given the wide variety of abnormal epigenetic marks that are possible targets for the advancement of anticancer therapy, the study of and application of epigenetic enzyme inhibitors for the anti-cancer therapy show promise[49,64].

Cell interactions and released substances can cause epigenetic alternations. It has been demonstrated that PDAC cells induced DNA methylation of the *SOCS1* gene, acytokine supressor and cancer promoting growth factor, to boost tumor cell proliferation *in vitro*[63,65]. Clinical evidences demonstrating a higher 3-mo overall survival in patients missing *SOCS1* methylationl end credence to this. In PDAC, lysine demethylase 3A (*KDM3A*) is an effective epigenetic regulator of immunotherapy responses. This enzyme controls the *EGFR* expressions[66]. Tumors produced by cancer cells deficient in *KDM3A* have infiltrating immune cells that are responsive to immunotherapy. To distinguish between PDAC and cancer precursor phase, methylation -specific electrophoresis was used to determine the methylation status of the *MUC1, MUC2,* and *MUC4* genes in pancreatic fluids[67]. Additionally, the methylation status of the mucin genes was examined

using machine learning, and it was discovered that *MUC1* and *MUC4* hypomethylation levels were significantly correlated with poor prognosis[68].

Through the suppression of Hedgehog (Hh) signaling, improved gemcitabine delivery was shown in preclinical investigations. Clinical studies were conducted for a number of cancers, but they were unsuccessful and did not progress to phase III trials[69]. However, preclinical research using epigenetic targeting of the proteins known as BET bromodomains, which controls the transcriptional output of Hh signaling, demonstrated positive results *in vitro,* suggesting possible synergistic therapeutic approaches[70]. BET bromodomain proteins are thought to be crucial contribution to PDAC development and are a topic of active investigations[71]. Based on the transcription factor GATA-binding factor 6 (*GATA6*)'s function as a regulator of the traditional PDAC subtype identity, the method to induce subtype switching in PDAC has been further investigated. A basal state is provided in PDAC by *GATA6* depletion[72]. As a regulator of *GATA6* transcription in PDAC, the histone methyltransferase zeste homologue 2 (*EZH2*) enhancer prevents the decreased *EZH2-GATA6* and induced gene signatures present in traditional PDAC subtypes. Therefore, a potential target for PDAC treatment in the future is the *EZH2-GATA6* axis[73]. Tazemetostat, an *EZH2* inhibitor, has been FDA-approved for use in the treatment of advanced epithelioid sarcoma and is currently being investigated in a phase II research in conjunction with ICI in the treatment of other solid tumors, including PDAC (NCT04705818)[74]. A hostile squamous cell subtype is promoted to differentiate in PDAC by epigenetic silencing of *GATA6*. Using genome-wide epigenetic mapping of the alterations 5-methylcytosine and 5-hydroxymethylcytosine (5hmC), this epigenetic dysregulation was demonstrated[75]. Due to decreased production of the enzyme 5-methylcytosine hydroxylase *TET2*, these transcriptional subtypes exhibit a higher loss of 5hmC. In addition, reduction of *SMAD4* expression revealed decreased 5hmC and *GATA6,* resulting in a more squamous-like tumor. Blocking DNA methylation by utilizing the DNA methyltransferase (DNMT) inhibitor 5-azacytidine slows the growth of typical PDAC tumor. In contrast, utilising the same medication or DNMT knockdown *via* small interfering RNA boosted hyaluronic acid synthesis, ultimately increasing the advancement of PDACI[76]. Epithelial cells from normal pancreata and PDAC underwent transcriptomic and DNA methylomic analysis, which identified a subpopulation characterised by hypomethylation of repetitive regions, which in turn triggers an interferon-linked transcriptional programme[77]. The relationship between cell-of-origin and epigenetics and tumor heterogeneity can be seen in the fact that tumors with low methylation were more aggressive than tumors with high methylation, which kept more of their cell-of-origin characteristics[78].

A clinical trial examining the medication in solid tumor types, including PDAC, and the recent FDA approval of the *EZH2* inhibitor tazemetostat for the treatment of advanced epithelioid sarcoma show a potential clinical relevance of the found *EZH2-GATA6* axis in PDAC tumor[79]. Numerous researches have examined how DNA methylation mechanisms control the expression of genes in various TME components[80]. For instance, 5-azacytidine, a DNA methyltransferase (DNMT) inhibitor, inhibited global DNA methylation in epithelial PDAC cells and cancer-associated fibroblasts (CAFs), which slowed the evolution of PDAC[75]. In immunocompetent PDAC models, DNMT inhibition increased CD4 and CD8 T-cell infiltration and significantly reduced tumor size. Espinet *et al*[77] have discovered a link between low DNA methylation levels and subpar PDAC patient outcomes. They show that tumors with low levels of overall DNA methylation in the epithelial cells exhibit increased expression of endogenous retroviral transcripts, robust double-stranded RNA sensing machinery engagement, activation of an interferon signature, and stromal cell reprogramming that is pro-tumourigenic in the PDAC TME. Clinical trials for a sequential strategy based on HDAC/DNMT inhibition, chemotherapy, and then PD-L1 blocking are now being conducted in PDAC, and the findings are highly anticipated[81].

Specifically, nucleoside-like inhibitors induce cytotoxicity through DNA damage brought on by the creation of DNMT-DNA abducts, disrupt DNA methylation, and encourage the re-expression of dormant genes. Both outcomes support anticancer action[82]. Additionally, RNA modification of N6-methyladenosine (m6A) is a unique strategy for dynamic and reversible epigenetic control that has been discovered by researchers. By triggering the Wnt signaling cascade and changing Wnt I[82].

Inhibitory factor 1 (*WIF-1*), m6A accelerates the course of PanCa. Demethylase, m6A rubber, and the alkylation repair protein 5 (*ALKBH5*) homolog are increased in gemcitabine-treated sensitized PDAC cells. By demethylating m6A and consequently reducing *WIF-1* and deactivating Wnt signaling, it slows the growth of tumors. *In vitro* and *in vivo* development and invasiveness are accelerated when PanCa cells lack *ALKBH5*[42,83]. As a result, *ALKBH5* might be a brand-new target for PanCa treatment. Numerous studies have shown how DNMT inhibitors affect PanCa cell lines *in vitro* by inhibiting them, radiosensitizing them, and immunological sensitizing them. PanCa DNA repair regulation is mediated by H3K36 methylation. H3K36 is a SETD2-dependent protein that is essential for HR repair. Demethylating H3K36 by demethylase *KDM4A* alters heart rate. A transcription factor for *MHCII, RFXAP* has been linked to the inhibition of tumor growth. PDAC survival was favourably linked with *RFXAP* deficiency[84]. Ding *et al*[85] found that the natural flavonoid fisetin regulates H3K36 methylation to promote *RFXAP* and *KDM4A* expression and interferes with HR, leading to DNA damage and PDAC S-phase arrest[85]. Therefore, this tactic may constitute a cutting-edge therapeutic method for treating PanCa. DNMT inhibitors (DNMTis) are undertaking Phase I/II clinical trials in patients with PanCa and have been shown to sensitize PDAC cells to immune checkpoint blockade treatment and chemotherapy [86]. Decitabine, alongside 5-aza, and guadecitabine are DNMTs used for PDAC. Haematological malignancies are also accepted to be treated with HDAC inhibitors (HDACis)[87]. Another therapeutic epigenetic approach for PanCa patients is HDAC inhibition. In PanCa cells, HDAC is, which includes *SAHA* and *CUDC-101*, can downregulate apoptotic inhibitory proteins including survivin and XIAP. Additionally, these HDACs can make PanCa more radiosensitive and make it cytotoxic[88]. AR-42, which is another potent HDACi against PanCa cells, can inhibit cell proliferation *via* inducing cell cycle arrest at G2 phase. Additionally, it can induce DNA damage, apoptosis, and p53 expression, suggesting that it may have therapeutic promise for the treatment of PanCa[89]. In addition to that, reader proteins with different bromodomains that attract proteins implicated in tumor initiation and elongation are blocked by the BET inhibitor JQ1 from binding to the BET domain. In the framework of personalized medicine, Bian *et al*[90] defined a novel

technique for PDAC classification and management based on sensitivity to JQ1 treatment. In order to select PanCa patients with unregulated c-MYC signaling pathways and demonstrate that these selected tumors exhibited greater susceptibility to BET inhibitor JQ1 treatment, the technique involved molecularly characterizing patient xenografts. According to the study, administering BET inhibitors in conjunction with conventional anticancer regimens may constitute an efficient therapy option for individuals who have been carefully chosen and categorized (Table 2)[83,91].

Mechanisms of faulty negative control of cell proliferation, in particular immune evasion, can also produce abnormal proliferation in the development of gastrointestinal malignancies, in addition to unchecked proliferation brought on by cell cycle dysregulation[92]. For instance, it was discovered by researchers that during PanCa, H3K4me3 of the *BCL2L1, CFLAR,* and *MCL-1* gene promoters upregulates the production of the anti-apoptotic proteins *Bcl-x, FLIP*, and *MCL-1,* as well as the *BAK1, BAX,* and *BCL2L11* gene promoters of Bak and Bax. Proapoptotic proteins like the Bim protein, for example, have their expression downregulated[93]. These six apoptosis-controlling genes are all essential for PanCa growth and development[94].

Initial investigations with human pancreatic cell lines showed that silencing *KMT2D* lowered the number and proportion of cells in G0/G1, which was accompanied by a drop in H3K4me1/2/3, indicating that histone methylation is actually involved in cells cycle management[95]. Further research has primarily focused on CKI control. *P15* and *P21* genes, which encode two often reported CKIs, show higher levels of H3K27me3 and H3K9me3 and lower levels of H3K4me2/3 in gastrointestinal malignancies such as GC, CRC, HCC, and PanCa[96]. Upstream lncRNAs such as *BLACAT1, SNHG17,* and *CASC15* can decrease P15 and P21 expression and cause G0/G1 checkpoint deficit. DZNep (3-deazaneplanocin A), a powerful pharmacologic inhibitor of S-adenosylhomocysteine hydrolase, modifies chromatin accessibility *via* inhibiting histone methyltransferases such as *EZH2*[97,98]. It results in a large decrease in H3K27me3 (a primary repressive histone mark) levels, as well as a significant decrease in cell proliferation and migration in CRC. Similar effects can be seen in PanCa, with decreased global H3K27me3 levels leading to re-expression of miR-218, limiting cell growth, encouraging apoptosis, and finally triggering cell cycle arrest in PanCa cells[99]. Another study found that DZNep significantly modulates miR-663a and miR-4787-5p expression and consecutively suppresses TGFb1-induced EMT signaling in PanCa[98,100]. UNC1999, an EZH2-specific inhibitor, not only lowers the abnormal H3K27 methylation that characterizes PanCa cells, but it also slows cancer cell proliferation in three model systems[101]. Furthermore, chaetospirolactone has been shown to suppress the activity of the epigenetic regulator *EZH2* and consistently decrease H3K27me3 to allow for the transcription of *DR4*, which then binds to TRAIL and culminates in the activation of initiator caspase-8 and the formation of the death-inducing signaling complex[102]. As a result, diosgenin, garcinol, *FBW7* and curcumin analogue CDF have also been identified as potential agents targeting *EZH2* to prevent the development of PanCa[97,103]. Amalgamation treatment with the HMT inhibitor panH3K9me chaetocin and an aurorakinase A (*AURKA*) inhibitor reduces H3K9 methylation at the centrosome, generating mitotic abnormalities that eventually drive aberrant mitotic checkpoint responses and eventually mitotic catastrophe in PanCa[104].

CONCLUSION

Since PanCa patients have a dismal prognosis, understanding the molecular events that drive this terrible tumor disease is critical for developing alternative and more effective treatment regimens and determining trustworthy diagnostic indicators. The role of epigenetics in the initiation, development, and evolution of PDAC has been demonstrated by advances in high throughput sequencing and genome-wide association studies. This review covers the major epigenetic signaling pathways as well as how the epigenetic machinery is altered or 'hijacked' in PanCa. Recent epigenetic research has considerably expanded our understanding of the regulatory characteristics involved in PanCa initiation, and progression, along with metastasis tumor. As discussed in this article, DNA-based epigenetic processes have been shown to play a role in PanCa and may serve as potential therapeutic targets aimed at rectifying epigenetic dysregulation of cellular machinery. Initial clinical trials with DNMT inhibitors at stages I-III are presently underway, paving the path for the creation of innovative, and hopefully more successful, 'epidrugs' for patients with PanCa. As a result, we believe that targeting epigenetic regulators and modulators with successful pharmaceutical or even immunotherapeutic techniques would be a game changer in the fight against this aggressive cancer. One significant restriction of using such epigenetic reprogramming of PDAC tumors is the danger of pleiotropic effects, which occur when certain components of the epigenetic machinery have opposite effects in different cellular compartments. Recent improvements in single-cell sequencing technologies that provide multi-omics information from the genome and transcriptome may be useful in determining the specific involvement of the several players in the epigenetic regulation of PDAC tumors. Overall, manipulating the epigenetic machinery, either alone or as part of a combination treatment plan, has the potential to reprogram the aggressive PDAC tumor profile to a less aggressive or easily identifiable and curable state, thereby benefiting patients in the future. In conclusion, we conclude that when cancer-associated signaling pathways are evaluated as a combined shift in "genomic-epigenomic-and-nuclear" structure, an even more realistic picture of PanCa will be obtained. Early preneoplastic lesions in this organ appear to require only a few mutations to initiate a process of aberrant organogenesis *via* self-reinforcing pathological loops. During metastatic progression, epigenomic landscapes defined by the differential acquisition of enhancers and super-enhancers appear to be required to maintain inheritable, cancer-associated gene expression patterns that support the heterogeneous differentiation of human PanCa tumors. This has given unique insights into an arsenal of novel, potentially actionable signaling pathways that were not previously achieved through genomic analyses, supporting the notion that effective future PDAC therapeutic regimens will require precision medicine approaches that include epigenomic targets.

Table 2 Current ongoing trails targeting epigenetic therapy (combination drugs) in Pancreatic Cancer

Drug names	Combination agents	Trail phase	NCT number
Panobinostat vorinostat	Various antineoplastic drugs	Phase 1	NCT03878524
Vorinostat	Capecitabine + radiation	Phase 1/2	NCT00948688
Tazemetostat	Durvalumab/gemcitabine	Phase 2 recruiting	NCT04705818
Durvalumab	Tazemetostat	Phase 2	NCT04705818
Romidepsin, azacitidine	Durvalumab, lenalidomide, nab-paclitaxel	Phase 1/2 recruiting	NCT04257448
Azacitidine	Chemotherapy after progression	Phase 2 active	NCT01845805
Vorinostat	Gemcitabine, sorafenib +/−, radiation	Phase 1 active	NCT02349867
CC-486 (oral azacitidine)	–	Phase 2 active	NCT01845805
Azacitidine, not recruiting	Pembrolizumab	Phase 2 active	NCT03264404
Tazemetostat	Durvalumab	Phase 2	NCT04705818
MK-8628	-	Phase 1 completed	NCT02259114
Rx-3117	Nab-paclitaxel	1,2	NCT03189914
Entinostat	Nivolumab	Phase 2 completed	NCT03250273
Decitabine	Tetrahydrouridine	Phase 1 completed	NCT02847000
Vorinostat	Capecitabine	Phase 1 completed	NCT00983268
Azacitidine	nab-Paclitaxel, carboplatin	Phase 1 completed	NCT01478685
Vorinostat	NPI-0052 (marizomib)	Phase 1 completed	NCT00667082
Azacitidine	Pembrolizumab	Phase 2 recruiting	NCT03264404
Azacitidine	Abraxane, gemcitabine	Phase 2 active	NCT01845805
Entinostat	Nivolumab	Phase 2 active	NCT03250273

ACKNOWLEDGEMENTS

First, we would like to thank all the authors and clinicians whose valuable work has supported us in writing this review. Second, we also acknowledge clinicians from Tata Medical Center namely Dr. Paromita Roy along with clinicians from Apollo Multispecialty Hospital namely Dr. Sumit Gulati and Dr. Supriyo Ghatak. We would also like to thank Prof. Bitan Kumar Chattopadhay from Department of General Surgery, IPGMER & SSKM Hospital, Kolkata and Prof. Shibajyoti Ghosh from Department of General Surgery, Medical College and Hospital, Kolkata, India. Dr. Aniruddha Chatterjee would like to thank Rutherford Discovery Fellowship from the Royal Society of New Zealand, Department of Pathology, Dunedin School of Medicine, University of Otago for their support. The authors specifically thank and acknowledge Mr. Saraswan Sikdar.

FOOTNOTES

Author contributions: Bararia A, Das A, and Mitra S wrote the first draft of the paper and constructed the flow chart and tables; Chatterjee A, Banerjee S, and Sikdar N provided valuable input, suggestions, comments and guidance while writing the review manuscript and contributed to proofreading and editing; Sikdar N constructed, conceptualized, and edited the review manuscript.

Supported by the Department of Biotechnology, Government of India Grant Sanction, Ramalingaswami Re-entry Fellowship, No. RLS/BT/Re-entry/05/2012.

Conflict-of-interest statement: All the authors declare no conflicts of interest.

Country/Territory of origin: India

ORCID number: Akash Bararia 0000-0002-9069-3116; Amlan Das 0000-0002-9295-3743; Sangeeta Mitra 0000-0002-0651-2280; Sudeep Banerjee

0000-0002-3157-4184; Aniruddha Chatterjee 0000-0001-7276-2248; Nilabja Sikdar 0000-0003-4465-472X.

S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Ying L**, Sharma A, Chhoda A, Ruzgar N, Hasan N, Kwak R, Wolfgang CL, Wang TH, Kunstman JW, Salem RR, Wood LD, Iacobuzio-Donahue C, Schneider EB, Farrell JJ, Ahuja N. Methylation-based Cell-free DNA Signature for Early Detection of Pancreatic Cancer. *Pancreas* 2021; **50**: 1267-1273 [PMID: 34860810 DOI: 10.1097/MPA.0000000000001919]

2 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

3 **Bararia A**, Chakraborty P, Roy P, Chattopadhay BK, Das A, Chatterjee A, Sikdar N. Emerging role of non-invasive and liquid biopsy biomarkers in pancreatic cancer. *World J Gastroenterol* 2023; **29**: 2241-2260 [PMID: 37124888 DOI: 10.3748/wjg.v29.i15.2241]

4 **Thompson ED**, Roberts NJ, Wood LD, Eshleman JR, Goggins MG, Kern SE, Klein AP, Hruban RH. The genetics of ductal adenocarcinoma of the pancreas in the year 2020: dramatic progress, but far to go. *Mod Pathol* 2020; **33**: 2544-2563 [PMID: 32704031 DOI: 10.1038/s41379-020-0629-6]

5 **Chatterjee A**, Bararia A, Ganguly D, Mondal PK, Roy P, Banerjee S, Ghosh S, Gulati S, Ghatak S, Chattopadhay BK, Basu P, Chatterjee A, Sikdar N. DNA methylome in pancreatic cancer identified novel promoter hyper-methylation in NPY and FAIM2 genes associated with poor prognosis in Indian patient cohort. *Cancer Cell Int* 2022; **22**: 334 [PMID: 36329447 DOI: 10.1186/s12935-022-02737-1]

6 **Hu JX**, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F. Pancreatic cancer: A review of epidemiology, trend, and risk factors. *World J Gastroenterol* 2021; **27**: 4298-4321 [PMID: 34366606 DOI: 10.3748/wjg.v27.i27.4298]

7 **O'Neill RS**, Stoita A. Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket? *World J Gastroenterol* 2021; **27**: 4045-4087 [PMID: 34326612 DOI: 10.3748/wjg.v27.i26.4045]

8 **Khalaf N**, El-Serag HB, Abrams HR, Thrift AP. Burden of Pancreatic Cancer: From Epidemiology to Practice. *Clin Gastroenterol Hepatol* 2021; **19**: 876-884 [PMID: 32147593 DOI: 10.1016/j.cgh.2020.02.054]

9 **Schnelldorfer T**, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, Gullerud RE, Donohue JH, Nagorney DM, Farnell MB. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? *Ann Surg* 2008; **247**: 456-462 [PMID: 18376190 DOI: 10.1097/SLA.0b013e3181613142]

10 **Zhao Y**, Yang M, Wang S, Abbas SJ, Zhang J, Li Y, Shao R, Liu Y. An Overview of Epigenetic Methylation in Pancreatic Cancer Progression. *Front Oncol* 2022; **12**: 854773 [PMID: 35296007 DOI: 10.3389/fonc.2022.854773]

11 **Pandey S**, Gupta VK, Lavania SP. Role of epigenetics in pancreatic ductal adenocarcinoma. *Epigenomics* 2023; **15**: 89-110 [PMID: 36647796 DOI: 10.2217/epi-2022-0177]

12 **Zhang Z**, Zhu R, Sun W, Wang J, Liu J. Analysis of Methylation-driven Genes in Pancreatic Ductal Adenocarcinoma for Predicting Prognosis. *J Cancer* 2021; **12**: 6507-6518 [PMID: 34659542 DOI: 10.7150/jca.53208]

13 **Visani M**, Acquaviva G, De Leo A, Sanza V, Merlo L, Maloberti T, Brandes AA, Franceschi E, Di Battista M, Masetti M, Jovine E, Fiorino S, Pession A, Tallini G, de Biase D. Molecular alterations in pancreatic tumors. *World J Gastroenterol* 2021; **27**: 2710-2726 [PMID: 34135550 DOI: 10.3748/wjg.v27.i21.2710]

14 **Brancaccio M**, Natale F, Falco G, Angrisano T. Cell-Free DNA Methylation: The New Frontiers of Pancreatic Cancer Biomarkers' Discovery. *Genes (Basel)* 2019; **11** [PMID: 31877923 DOI: 10.3390/genes11010014]

15 **Thompson MJ**, Rubbi L, Dawson DW, Donahue TR, Pellegrini M. Pancreatic cancer patient survival correlates with DNA methylation of pancreas development genes. *PLoS One* 2015; **10**: e0128814 [PMID: 26039411 DOI: 10.1371/journal.pone.0128814]

16 **Thompson JK**, Bednar F. Clinical Utility of Epigenetic Changes in Pancreatic Adenocarcinoma. *Epigenomes* 2021; **5** [PMID: 34968245 DOI: 10.3390/epigenomes5040020]

17 **Bararia A**, Dey S, Gulati S, Ghatak S, Ghosh S, Banerjee S, Sikdar N. Differential methylation landscape of pancreatic ductal adenocarcinoma and its precancerous lesions. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 205-217 [PMID: 32312637 DOI: 10.1016/j.hbpd.2020.03.010]

18 **Wang SS**, Xu J, Ji KY, Hwang CI. Epigenetic Alterations in Pancreatic Cancer Metastasis. *Biomolecules* 2021; **11** [PMID: 34439749 DOI: 10.3390/biom11081082]

19 **Neureiter D**, Jäger T, Ocker M, Kiesslich T. Epigenetics and pancreatic cancer: pathophysiology and novel treatment aspects. *World J Gastroenterol* 2014; **20**: 7830-7848 [PMID: 24976721 DOI: 10.3748/wjg.v20.i24.7830]

20 **Zamboni G**, Hirabayashi K, Castelli P, Lennon AM. Precancerous lesions of the pancreas. *Best Pract Res Clin Gastroenterol* 2013; **27**: 299-322 [PMID: 23809247 DOI: 10.1016/j.bpg.2013.04.001]

21 **Guler GD**, Ning Y, Ku CJ, Phillips T, McCarthy E, Ellison CK, Bergamaschi A, Collin F, Lloyd P, Scott A, Antoine M, Wang W, Chau K, Ashworth A, Quake SR, Levy S. Detection of early stage pancreatic cancer using 5-hydroxymethylcytosine signatures in circulating cell free DNA. *Nat Commun* 2020; **11**: 5270 [PMID: 33077732 DOI: 10.1038/s41467-020-18965-w]

22 **Fujikura K**, Alruwaii ZI, Haffner MC, Trujillo MA, Roberts NJ, Hong SM, Macgregor-Das A, Goggins MG, Roy S, Meeker AK, Ding D, Wright M, He J, Hruban RH, Wood LD. Downregulation of 5-hydroxymethylcytosine is an early event in pancreatic tumorigenesis. *J Pathol* 2021; **254**: 279-288 [PMID: 33870509 DOI: 10.1002/path.5682]

23 **Lomberk G**, Dusetti N, Iovanna J, Urrutia R. Emerging epigenomic landscapes of pancreatic cancer in the era of precision medicine. *Nat Commun* 2019; **10**: 3875 [PMID: 31462645 DOI: 10.1038/s41467-019-11812-7]

24 **Michael JV**, Goldfinger LE. Concepts and advances in cancer therapeutic vulnerabilities in RAS membrane targeting. *Semin Cancer Biol* 2019; **54**: 121-130 [PMID: 29203271 DOI: 10.1016/j.semcancer.2017.11.021]

25 **Saha G**, Singh R, Mandal A, Das S, Chattopadhyay E, Panja P, Roy P, DeSarkar N, Gulati S, Ghatak S, Ghosh S, Banerjee S, Roy B, Chaudhuri D, Arora N, Biswas NK, Sikdar N. A novel hotspot and rare somatic mutation p.A138V, at TP53 is associated with poor survival of

pancreatic ductal and periampullary adenocarcinoma patients. *Mol Med* 2020; **26**: 59 [PMID: 32552660 DOI: 10.1186/s10020-020-00183-1]

26 **Choi M**, Bien H, Mofunanya A, Powers S. Challenges in Ras therapeutics in pancreatic cancer. *Semin Cancer Biol* 2019; **54**: 101-108 [PMID: 29170065 DOI: 10.1016/j.semcancer.2017.11.015]

27 **Canon J**, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, Gaida K, Holt T, Knutson CG, Koppada N, Lanman BA, Werner J, Rapaport AS, San Miguel T, Ortiz R, Osgood T, Sun JR, Zhu X, McCarter JD, Volak LP, Houk BE, Fakih MG, O'Neil BH, Price TJ, Falchook GS, Desai J, Kuo J, Govindan R, Hong DS, Ouyang W, Henary H, Arvedson T, Cee VJ, Lipford JR. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* 2019; **575**: 217-223 [PMID: 31666701 DOI: 10.1038/s41586-019-1694-1]

28 **Seton-Rogers S**. KRAS-G12C in the crosshairs. *Nat Rev Cancer* 2020; **20**: 3 [PMID: 31728026 DOI: 10.1038/s41568-019-0228-3]

29 **Bryant KL**, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, Gunda V, Pierobon M, Waters AM, George SD, Tomar G, Papke B, Hobbs GA, Yan L, Hayes TK, Diehl JN, Goode GD, Chaika NV, Wang Y, Zhang GF, Witkiewicz AK, Knudsen ES, Petricoin EF 3rd, Singh PK, Macdonald JM, Tran NL, Lyssiotis CA, Ying H, Kimmelman AC, Cox AD, Der CJ. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. *Nat Med* 2019; **25**: 628-640 [PMID: 30833752 DOI: 10.1038/s41591-019-0368-8]

30 **Fitzgerald TL**, Lertpiriyapong K, Cocco L, Martelli AM, Libra M, Candido S, Montalto G, Cervello M, Steelman L, Abrams SL, McCubrey JA. Roles of EGFR and KRAS and their downstream signaling pathways in pancreatic cancer and pancreatic cancer stem cells. *Adv Biol Regul* 2015; **59**: 65-81 [PMID: 26257206 DOI: 10.1016/j.jbior.2015.06.003]

31 **Ardito CM**, Grüner BM, Takeuchi KK, Lubeseder-Martellato C, Teichmann N, Mazur PK, Delgiorno KE, Carpenter ES, Halbrook CJ, Hall JC, Pal D, Briel T, Herner A, Trajkovic-Arsic M, Sipos B, Liou GY, Storz P, Murray NR, Threadgill DW, Sibilia M, Washington MK, Wilson CL, Schmid RM, Raines EW, Crawford HC, Siveke JT. EGF receptor is required for KRAS-induced pancreatic tumorigenesis. *Cancer Cell* 2012; **22**: 304-317 [PMID: 22975374 DOI: 10.1016/j.ccr.2012.07.024]

32 **Zhan T**, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene* 2017; **36**: 1461-1473 [PMID: 27617575 DOI: 10.1038/onc.2016.304]

33 **Davis SL**, Cardin DB, Shahda S, Lenz HJ, Dotan E, O'Neil BH, Kapoun AM, Stagg RJ, Berlin J, Messersmith WA, Cohen SJ. A phase 1b dose escalation study of Wnt pathway inhibitor vantictumab in combination with nab-paclitaxel and gemcitabine in patients with previously untreated metastatic pancreatic cancer. *Invest New Drugs* 2020; **38**: 821-830 [PMID: 31338636 DOI: 10.1007/s10637-019-00824-1]

34 **Deplanque G**, Demarchi M, Hebbar M, Flynn P, Melichar B, Atkins J, Nowara E, Moyé L, Piquemal D, Ritter D, Dubreuil P, Mansfield CD, Acin Y, Moussy A, Hermine O, Hammel P. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. *Ann Oncol* 2015; **26**: 1194-1200 [PMID: 25858497 DOI: 10.1093/annonc/mdv133]

35 **Fang YT**, Yang WW, Niu YR, Sun YK. Recent advances in targeted therapy for pancreatic adenocarcinoma. *World J Gastrointest Oncol* 2023; **15**: 571-595 [PMID: 37123059 DOI: 10.4251/wjgo.v15.i4.571]

36 **Li Q**, Li Z, Luo T, Shi H. Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy. *Mol Biomed* 2022; **3**: 47 [PMID: 36539659 DOI: 10.1186/s43556-022-00110-2]

37 **Karar J**, Maity A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front Mol Neurosci* 2011; **4**: 51 [PMID: 22144946 DOI: 10.3389/fnmol.2011.00051]

38 **Takeda H**, Rust AG, Ward JM, Yew CC, Jenkins NA, Copeland NG. Sleeping Beauty transposon mutagenesis identifies genes that cooperate with mutant Smad4 in gastric cancer development. *Proc Natl Acad Sci U S A* 2016; **113**: E2057-E2065 [PMID: 27006499 DOI: 10.1073/pnas.1603223113]

39 **Vincent A**, Omura N, Hong SM, Jaffe A, Eshleman J, Goggins M. Genome-wide analysis of promoter methylation associated with gene expression profile in pancreatic adenocarcinoma. *Clin Cancer Res* 2011; **17**: 4341-4354 [PMID: 21610144 DOI: 10.1158/1078-0432.CCR-10-3431]

40 **di Magliano MP**, Logsdon CD. Roles for KRAS in pancreatic tumor development and progression. *Gastroenterology* 2013; **144**: 1220-1229 [PMID: 23622131 DOI: 10.1053/j.gastro.2013.01.071]

41 **Fukushima N**, Sato N, Ueki T, Rosty C, Walter KM, Wilentz RE, Yeo CJ, Hruban RH, Goggins M. Aberrant methylation of preproenkephalin and p16 genes in pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma. *Am J Pathol* 2002; **160**: 1573-1581 [PMID: 12000709 DOI: 10.1016/S0002-9440(10)61104-2]

42 **Tang B**, Yang Y, Kang M, Wang Y, Bi Y, He S, Shimamoto F. m(6)A demethylase ALKBH5 inhibits pancreatic cancer tumorigenesis by decreasing WIF-1 RNA methylation and mediating Wnt signaling. *Mol Cancer* 2020; **19**: 3 [PMID: 31906946 DOI: 10.1186/s12943-019-1128-6]

43 **Jones S**, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321**: 1801-1806 [PMID: 18772397 DOI: 10.1126/science.1164368]

44 **Li X**, Zhang X, Lin X, Cai L, Wang Y, Chang Z. Classification and Prognosis Analysis of Pancreatic Cancer Based on DNA Methylation Profile and Clinical Information. *Genes (Basel)* 2022; **13** [PMID: 36292798 DOI: 10.3390/genes13101913]

45 **Xiao M**, Liang X, Yan Z, Chen J, Zhu Y, Xie Y, Li Y, Li X, Gao Q, Feng F, Fu G, Gao Y. A DNA-Methylation-Driven Genes Based Prognostic Signature Reveals Immune Microenvironment in Pancreatic Cancer. *Front Immunol* 2022; **13**: 803962 [PMID: 35222383 DOI: 10.3389/fimmu.2022.803962]

46 **Zou T**, Shi D, Wang W, Chen G, Zhang X, Tian Y, Gong P. Identification of a New m6A Regulator-Related Methylation Signature for Predicting the Prognosis and Immune Microenvironment of Patients with Pancreatic Cancer. *Mediators Inflamm* 2023; **2023**: 5565054 [PMID: 37181810 DOI: 10.1155/2023/5565054]

47 **Zheng X**, Du Y, Liu M, Wang C. ITGA3 acts as a purity-independent biomarker of both immunotherapy and chemotherapy resistance in pancreatic cancer: bioinformatics and experimental analysis. *Funct Integr Genomics* 2023; **23**: 196 [PMID: 37270717 DOI: 10.1007/s10142-023-01122-z]

48 **Nones K**, Waddell N, Song S, Patch AM, Miller D, Johns A, Wu J, Kassahn KS, Wood D, Bailey P, Fink L, Manning S, Christ AN, Nourse C, Kazakoff S, Taylor D, Leonard C, Chang DK, Jones MD, Thomas M, Watson C, Pinese M, Cowley M, Rooman I, Pajic M; APGI, Butturini G, Malpaga A, Corbo V, Crippa S, Falconi M, Zamboni G, Castelli P, Lawlor RT, Gill AJ, Scarpa A, Pearson JV, Biankin AV, Grimmond SM. Genome-wide DNA methylation patterns in pancreatic ductal adenocarcinoma reveal epigenetic deregulation of SLIT-ROBO, ITGA2 and MET signaling. *Int J Cancer* 2014; **135**: 1110-1118 [PMID: 24500968 DOI: 10.1002/ijc.28765]

49 **Paradise BD**, Barham W, Fernandez-Zapico ME. Targeting Epigenetic Aberrations in Pancreatic Cancer, a New Path to Improve Patient Outcomes? *Cancers (Basel)* 2018; **10** [PMID: 29710783 DOI: 10.3390/cancers10050128]

50 **House MG**, Guo M, Iacobuzio-Donahue C, Herman JG. Molecular progression of promoter methylation in intraductal papillary mucinous neoplasms (IPMN) of the pancreas. *Carcinogenesis* 2003; **24**: 193-198 [PMID: 12584167 DOI: 10.1093/carcin/24.2.193]

51 **Grzenda A**, Ordog T, Urrutia R. Polycomb and the emerging epigenetics of pancreatic cancer. *J Gastrointest Cancer* 2011; **42**: 100-111 [PMID: 21336826 DOI: 10.1007/s12029-011-9262-4]

52 **Hamano H**, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**: 732-738 [PMID: 11236777 DOI: 10.1056/NEJM200103083441005]

53 **Umehara H**, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Sumida T, Mimori T, Tanaka Y, Tsubota K, Yoshino T, Kawa S, Suzuki R, Takegami T, Tomosugi N, Kurose N, Ishigaki Y, Azumi A, Kojima M, Nakamura S, Inoue D; Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2012; **22**: 1-14 [PMID: 21881964 DOI: 10.1007/s10165-011-0508-6]

54 **Kinugawa Y**, Uehara T, Matsuda K, Kobayashi Y, Nakajima T, Hamano H, Kawa S, Higuchi K, Hosaka N, Shiozawa S, Ishigame H, Nakamura T, Maruyama Y, Nakazawa K, Nakaguro M, Sano K, Ota H. Promoter hypomethylation of SKI in autoimmune pancreatitis. *Pathol Res Pract* 2018; **214**: 492-497 [PMID: 29534839 DOI: 10.1016/j.prp.2018.03.005]

55 **Zhang CY**, Liu S, Yang M. Clinical diagnosis and management of pancreatic cancer: Markers, molecular mechanisms, and treatment options. *World J Gastroenterol* 2022; **28**: 6827-6845 [PMID: 36632312 DOI: 10.3748/wjg.v28.i48.6827]

56 **Jamieson NB**, Steele CW. Immuno-Oncology in Pancreatic Cancer. In: Textbook of Pancreatic Cancer. Cham: Springer International Publishing, 2021: 287–304 [DOI: 10.1007/978-3-030-53786-9_20]

57 **Bailey P**, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, Nourse C, Murtaugh LC, Harliwong I, Idrisoglu S, Manning S, Nourbakhsh E, Wani S, Fink L, Holmes O, Chin V, Anderson MJ, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Xu Q, Wilson PJ, Cloonan N, Kassahn KS, Taylor D, Quek K, Robertson A, Pantano L, Mincarelli L, Sanchez LN, Evers L, Wu J, Pinese M, Cowley MJ, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chantrill LA, Mawson A, Humphris J, Chou A, Pajic M, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Lovell JA, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Moran-Jones K, Jamieson NB, Graham JS, Duthie F, Oien K, Hair J, Grützmann R, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Rusev B, Capelli P, Salvia R, Tortora G, Mukhopadhyay D, Petersen GM; Australian Pancreatic Cancer Genome Initiative, Munzy DM, Fisher WE, Karim SA, Eshleman JR, Hruban RH, Pilarsky C, Morton JP, Sansom OJ, Scarpa A, Musgrove EA, Bailey UM, Hofmann O, Sutherland RL, Wheeler DA, Gill AJ, Gibbs RA, Pearson JV, Waddell N, Biankin AV, Grimmond SM. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016; **531**: 47-52 [PMID: 26909576 DOI: 10.1038/nature16965]

58 **Moffitt RA**, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, Rashid NU, Williams LA, Eaton SC, Chung AH, Smyla JK, Anderson JM, Kim HJ, Bentrem DJ, Talamonti MS, Iacobuzio-Donahue CA, Hollingsworth MA, Yeh JJ. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat Genet* 2015; **47**: 1168-1178 [PMID: 26343385 DOI: 10.1038/ng.3398]

59 **Malinova A**, Veghini L, Real FX, Corbo V. Cell Lineage Infidelity in PDAC Progression and Therapy Resistance. *Front Cell Dev Biol* 2021; **9**: 795251 [PMID: 34926472 DOI: 10.3389/fcell.2021.795251]

60 **Koni M**, Pinnarò V, Brizzi MF. The Wnt Signalling Pathway: A Tailored Target in Cancer. *Int J Mol Sci* 2020; **21** [PMID: 33080952 DOI: 10.3390/ijms21207697]

61 **Kirkegård J**, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. *Am J Gastroenterol* 2017; **112**: 1366-1372 [PMID: 28762376 DOI: 10.1038/ajg.2017.218]

62 **Del Poggetto E**, Ho IL, Balestrieri C, Yen EY, Zhang S, Citron F, Shah R, Corti D, Diaferia GR, Li CY, Loponte S, Carbone F, Hayakawa Y, Valenti G, Jiang S, Sapio L, Jiang H, Dey P, Gao S, Deem AK, Rose-John S, Yao W, Ying H, Rhim AD, Genovese G, Heffernan TP, Maitra A, Wang TC, Wang L, Draetta GF, Carugo A, Natoli G, Viale A. Epithelial memory of inflammation limits tissue damage while promoting pancreatic tumorigenesis. *Science* 2021; **373**: eabj0486 [PMID: 34529467 DOI: 10.1126/science.abj0486]

63 **Garcia-Gomez A**, Rodríguez-Ubreva J, Ballestar E. Epigenetic interplay between immune, stromal and cancer cells in the tumor microenvironment. *Clin Immunol* 2018; **196**: 64-71 [PMID: 29501540 DOI: 10.1016/j.clim.2018.02.013]

64 **Natale F**, Vivo M, Falco G, Angrisano T. Deciphering DNA methylation signatures of pancreatic cancer and pancreatitis. *Clin Epigenetics* 2019; **11**: 132 [PMID: 31492175 DOI: 10.1186/s13148-019-0728-8]

65 **Xiao Q**, Zhou D, Rucki AA, Williams J, Zhou J, Mo G, Murphy A, Fujiwara K, Kleponis J, Salman B, Wolfgang CL, Anders RA, Zheng S, Jaffee EM, Zheng L. Cancer-Associated Fibroblasts in Pancreatic Cancer Are Reprogrammed by Tumor-Induced Alterations in Genomic DNA Methylation. *Cancer Res* 2016; **76**: 5395-5404 [PMID: 27496707 DOI: 10.1158/0008-5472.CAN-15-3264]

66 **Li J**, Yuan S, Norgard RJ, Yan F, Sun YH, Kim IK, Merrell AJ, Sela Y, Jiang Y, Bhanu NV, Garcia BA, Vonderheide RH, Blanco A, Stanger BZ. Epigenetic and Transcriptional Control of the Epidermal Growth Factor Receptor Regulates the Tumor Immune Microenvironment in Pancreatic Cancer. *Cancer Discov* 2021; **11**: 736-753 [PMID: 33158848 DOI: 10.1158/2159-8290.CD-20-0519]

67 **Yokoyama S**, Kitamoto S, Higashi M, Goto Y, Hara T, Ikebe D, Yamaguchi T, Arisaka Y, Niihara T, Nishimata H, Tanaka S, Takaori K, Batra SK, Yonezawa S. Diagnosis of pancreatic neoplasms using a novel method of DNA methylation analysis of mucin expression in pancreatic juice. *PLoS One* 2014; **9**: e93760 [PMID: 24714692 DOI: 10.1371/journal.pone.0093760]

68 **Yokoyama S**, Hamada T, Higashi M, Matsuo K, Maemura K, Kurahara H, Horinouchi M, Hiraki T, Sugimoto T, Akahane T, Yonezawa S, Kornmann M, Batra SK, Hollingsworth MA, Tanimoto A. Predicted Prognosis of Patients with Pancreatic Cancer by Machine Learning. *Clin Cancer Res* 2020; **26**: 2411-2421 [PMID: 31992588 DOI: 10.1158/1078-0432.CCR-19-1247]

69 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461 [PMID: 19460966 DOI: 10.1126/science.1171362]

70 **Huang Y**, Nahar S, Nakagawa A, Fernandez-Barrena MG, Mertz JA, Bryant BM, Adams CE, Mino-Kenudson M, Von Alt KN, Chang K, Conery AR, Hatton C, Sims RJ 3rd, Fernandez-Zapico ME, Wang X, Lillemoe KD, Fernández-Del Castillo C, Warshaw AL, Thayer SP, Liss AS. Regulation of GLI Underlies a Role for BET Bromodomains in Pancreatic Cancer Growth and the Tumor Microenvironment. *Clin Cancer Res* 2016; **22**: 4259-4270 [PMID: 27169995 DOI: 10.1158/1078-0432.CCR-15-2068]

71 **Smith SG**, Zhou MM. The Bromodomain: A New Target in Emerging Epigenetic Medicine. *ACS Chem Biol* 2016; **11**: 598-608 [PMID:

26596782 DOI: 10.1021/acschembio.5b00831]

72 **Lomberk G**, Blum Y, Nicolle R, Nair A, Gaonkar KS, Marisa L, Mathison A, Sun Z, Yan H, Elarouci N, Armenoult L, Ayadi M, Ordog T, Lee JH, Oliver G, Klee E, Moutardier V, Gayet O, Bian B, Duconseil P, Gilabert M, Bigonnet M, Garcia S, Turrini O, Delpero JR, Giovannini M, Grandval P, Gasmi M, Secq V, De Reyniès A, Dusetti N, Iovanna J, Urrutia R. Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes. *Nat Commun* 2018; **9**: 1978 [PMID: 29773832 DOI: 10.1038/s41467-018-04383-6]

73 **Kloesch B**, Ionasz V, Paliwal S, Hruschka N, Martinez de Villarreal J, Öllinger R, Mueller S, Dienes HP, Schindl M, Gruber ES, Stift J, Herndler-Brandstetter D, Lomberk GA, Seidler B, Saur D, Rad R, Urrutia RA, Real FX, Martinelli P. A GATA6-centred gene regulatory network involving HNFs and ΔNp63 controls plasticity and immune escape in pancreatic cancer. *Gut* 2022; **71**: 766-777 [PMID: 33846140 DOI: 10.1136/gutjnl-2020-321397]

74 **Eyres M**, Lanfredini S, Xu H, Burns A, Blake A, Willenbrock F, Goldin R, Hughes D, Hughes S, Thapa A, Vavoulis D, Hubert A, D'Costa Z, Sabbagh A, Abraham AG, Blancher C, Jones S, Verrill C, Silva M, Soonawalla Z, Maughan T, Schuh A, Mukherjee S, O'Neill E. TET2 Drives 5hmc Marking of GATA6 and Epigenetically Defines Pancreatic Ductal Adenocarcinoma Transcriptional Subtypes. *Gastroenterology* 2021; **161**: 653-668.e16 [PMID: 33915173 DOI: 10.1053/j.gastro.2021.04.044]

75 **Shakya R**, Gonda T, Quante M, Salas M, Kim S, Brooks J, Hirsch S, Davies J, Cullo A, Olive K, Wang TC, Szabolcs M, Tycko B, Ludwig T. Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma. *Cancer Res* 2013; **73**: 885-896 [PMID: 23204224 DOI: 10.1158/0008-5472.CAN-12-1880]

76 **Kohi S**, Sato N, Cheng XB, Koga A, Higure A, Hirata K. A novel epigenetic mechanism regulating hyaluronan production in pancreatic cancer cells. *Clin Exp Metastasis* 2016; **33**: 225-230 [PMID: 26589701 DOI: 10.1007/s10585-015-9771-9]

77 **Espinet E**, Gu Z, Imbusch CD, Giese NA, Büscher M, Safavi M, Weisenburger S, Klein C, Vogel V, Falcone M, Insua-Rodríguez J, Reitberger M, Thiel V, Kossi SO, Muckenhuber A, Sarai K, Lee AYL, Backx E, Zarei S, Gaida MM, Rodríguez-Paredes M, Donato E, Yen HY, Eils R, Schlesner M, Pfarr N, Hackert T, Plass C, Brors B, Steiger K, Weichenhan D, Arda HE, Rooman I, Kopp JL, Strobel O, Weichert W, Sprick MR, Trumpp A. Aggressive PDACs Show Hypomethylation of Repetitive Elements and the Execution of an Intrinsic IFN Program Linked to a Ductal Cell of Origin. *Cancer Discov* 2021; **11**: 638-659 [PMID: 33060108 DOI: 10.1158/2159-8290.CD-20-1202]

78 **Roalsø MTT**, Hald ØH, Alexeeva M, Søreide K. Emerging Role of Epigenetic Alterations as Biomarkers and Novel Targets for Treatments in Pancreatic Ductal Adenocarcinoma. *Cancers (Basel)* 2022; **14** [PMID: 35158814 DOI: 10.3390/cancers14030546]

79 **Patil S**, Steuber B, Kopp W, Kari V, Urbach L, Wang X, Küffer S, Bohnenberger H, Spyropoulou D, Zhang Z, Versemann L, Bösherz MS, Brunner M, Gaedcke J, Ströbel P, Zhang JS, Neesse A, Ellenrieder V, Singh SK, Johnsen SA, Hessmann E. EZH2 Regulates Pancreatic Cancer Subtype Identity and Tumor Progression *via* Transcriptional Repression of GATA6. *Cancer Res* 2020; **80**: 4620-4632 [PMID: 32907838 DOI: 10.1158/0008-5472.CAN-20-0672]

80 **Neesse A**, Bauer CA, Öhlund D, Lauth M, Buchholz M, Michl P, Tuveson DA, Gress TM. Stromal biology and therapy in pancreatic cancer: ready for clinical translation? *Gut* 2019; **68**: 159-171 [PMID: 30177543 DOI: 10.1136/gutjnl-2018-316451]

81 **Versemann L**, Hessmann E, Ulisse M. Epigenetic Therapeutic Strategies to Target Molecular and Cellular Heterogeneity in Pancreatic Cancer. *Visc Med* 2022; **38**: 11-19 [PMID: 35291698 DOI: 10.1159/000519859]

82 **Pechalrieu D**, Etievant C, Arimondo PB. DNA methyltransferase inhibitors in cancer: From pharmacology to translational studies. *Biochem Pharmacol* 2017; **129**: 1-13 [PMID: 27956110 DOI: 10.1016/j.bcp.2016.12.004]

83 **Ganji C**, Farran B. Current clinical trials for epigenetic targets and therapeutic inhibitors for pancreatic cancer therapy. *Drug Discov Today* 2022; **27**: 1404-1410 [PMID: 34952224 DOI: 10.1016/j.drudis.2021.12.013]

84 **Ettel M**, Zhao L, Schechter S, Shi J. Expression and prognostic value of NSD1 and SETD2 in pancreatic ductal adenocarcinoma and its precursor lesions. *Pathology* 2019; **51**: 392-398 [PMID: 31060750 DOI: 10.1016/j.pathol.2019.02.005]

85 **Ding G**, Xu X, Li D, Chen Y, Wang W, Ping D, Jia S, Cao L. Fisetin inhibits proliferation of pancreatic adenocarcinoma by inducing DNA damage *via* RFXAP/KDM4A-dependent histone H3K36 demethylation. *Cell Death Dis* 2020; **11**: 893 [PMID: 33093461 DOI: 10.1038/s41419-020-03019-2]

86 **Berdasco M**, Esteller M. Clinical epigenetics: seizing opportunities for translation. *Nat Rev Genet* 2019; **20**: 109-127 [PMID: 30479381 DOI: 10.1038/s41576-018-0074-2]

87 **Bennett RL**, Licht JD. Targeting Epigenetics in Cancer. *Annu Rev Pharmacol Toxicol* 2018; **58**: 187-207 [PMID: 28992434 DOI: 10.1146/annurev-pharmtox-010716-105106]

88 **Moertl S**, Payer S, Kell R, Winkler K, Anastasov N, Atkinson MJ. Comparison of Radiosensitization by HDAC Inhibitors CUDC-101 and SAHA in Pancreatic Cancer Cells. *Int J Mol Sci* 2019; **20** [PMID: 31269745 DOI: 10.3390/ijms20133259]

89 **De Souza C**, Chatterji BP. HDAC Inhibitors as Novel Anti-Cancer Therapeutics. *Recent Pat Anticancer Drug Discov* 2015; **10**: 145-162 [PMID: 25782916 DOI: 10.2174/1574892810666150317144511]

90 **Bian B**, Bigonnet M, Gayet O, Loncle C, Maignan A, Gilabert M, Moutardier V, Garcia S, Turrini O, Delpero JR, Giovannini M, Grandval P, Gasmi M, Ouaissi M, Secq V, Poizat F, Nicolle R, Blum Y, Marisa L, Rubis M, Raoul JL, Bradner JE, Qi J, Lomberk G, Urrutia R, Saul A, Dusetti N, Iovanna J. Gene expression profiling of patient-derived pancreatic cancer xenografts predicts sensitivity to the BET bromodomain inhibitor JQ1: implications for individualized medicine efforts. *EMBO Mol Med* 2017; **9**: 482-497 [PMID: 28275007 DOI: 10.15252/emmm.201606975]

91 **Bian B**, Juiz NA, Gayet O, Bigonnet M, Brandone N, Roques J, Cros J, Wang N, Dusetti N, Iovanna J. Pancreatic Cancer Organoids for Determining Sensitivity to Bromodomain and Extra-Terminal Inhibitors (BETi). *Front Oncol* 2019; **9**: 475 [PMID: 31231611 DOI: 10.3389/fonc.2019.00475]

92 **Lu C**, Yang D, Sabbatini ME, Colby AH, Grinstaff MW, Oberlies NH, Pearce C, Liu K. Contrasting roles of H3K4me3 and H3K9me3 in regulation of apoptosis and gemcitabine resistance in human pancreatic cancer cells. *BMC Cancer* 2018; **18**: 149 [PMID: 29409480 DOI: 10.1186/s12885-018-4061-y]

93 **Tan N**, Wong M, Nannini MA, Hong R, Lee LB, Price S, Williams K, Savy PP, Yue P, Sampath D, Settleman J, Fairbrother WJ, Belmont LD. Bcl-2/Bcl-xL inhibition increases the efficacy of MEK inhibition alone and in combination with PI3 kinase inhibition in lung and pancreatic tumor models. *Mol Cancer Ther* 2013; **12**: 853-864 [PMID: 23475955 DOI: 10.1158/1535-7163.MCT-12-0949]

94 **Abulwerdi F**, Liao C, Liu M, Azmi AS, Aboukameel A, Mady AS, Gulappa T, Cierpicki T, Owens S, Zhang T, Sun D, Stuckey JA, Mohammad RM, Nikolovska-Coleska Z. A novel small-molecule inhibitor of mcl-1 blocks pancreatic cancer growth in vitro and in vivo. *Mol Cancer Ther* 2014; **13**: 565-575 [PMID: 24019208 DOI: 10.1158/1535-7163.MCT-12-0767]

95 **Dawkins JB**, Wang J, Maniati E, Heward JA, Koniali L, Kocher HM, Martin SA, Chelala C, Balkwill FR, Fitzgibbon J, Grose RP. Reduced Expression of Histone Methyltransferases KMT2C and KMT2D Correlates with Improved Outcome in Pancreatic Ductal Adenocarcinoma.

Cancer Res 2016; **76**: 4861-4871 [PMID: 27280393 DOI: 10.1158/0008-5472.CAN-16-0481]

96 **Matsuura I**, Denissova NG, Wang G, He D, Long J, Liu F. Cyclin-dependent kinases regulate the antiproliferative function of Smads. *Nature* 2004; **430**: 226-231 [PMID: 15241418 DOI: 10.1038/nature02650]

97 **Batchu RB**, Qazi AM, Gruzdyn OV, Semaan A, Seward SM, Chamala S, Dhulipala VB, Bouwman DL, Weaver DW, Gruber SA. EZH2-shRNA-mediated upregulation of p21waf1/cip1 and its transcriptional enhancers with concomitant downmodulation of mutant p53 in pancreatic ductal adenocarcinoma. *Surgery* 2013; **154**: 739-46; discussion 746 [PMID: 24074410 DOI: 10.1016/j.surg.2013.06.041]

98 **Cheng Y**, He C, Wang M, Ma X, Mo F, Yang S, Han J, Wei X. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. *Signal Transduct Target Ther* 2019; **4**: 62 [PMID: 31871779 DOI: 10.1038/s41392-019-0095-0]

99 **Kato S**, Schwaederle M, Daniels GA, Piccioni D, Kesari S, Bazhenova L, Shimabukuro K, Parker BA, Fanta P, Kurzrock R. Cyclin-dependent kinase pathway aberrations in diverse malignancies: clinical and molecular characteristics. *Cell Cycle* 2015; **14**: 1252-1259 [PMID: 25695927 DOI: 10.1080/15384101.2015.1014149]

100 **Mody HR**, Hung SW, AlSaggar M, Griffin J, Govindarajan R. Inhibition of S-Adenosylmethionine-Dependent Methyltransferase Attenuates TGFβ1-Induced EMT and Metastasis in Pancreatic Cancer: Putative Roles of miR-663a and miR-4787-5p. *Mol Cancer Res* 2016; **14**: 1124-1135 [PMID: 27624777 DOI: 10.1158/1541-7786.MCR-16-0083]

101 **Huang L**, Holtzinger A, Jagan I, BeGora M, Lohse I, Ngai N, Nostro C, Wang R, Muthuswamy LB, Crawford HC, Arrowsmith C, Kalloger SE, Renouf DJ, Connor AA, Cleary S, Schaeffer DF, Roehrl M, Tsao MS, Gallinger S, Keller G, Muthuswamy SK. Ductal pancreatic cancer modeling and drug screening using human pluripotent stem cell- and patient-derived tumor organoids. *Nat Med* 2015; **21**: 1364-1371 [PMID: 26501191 DOI: 10.1038/nm.3973]

102 **Hu W**, Jia X, Gao Y, Zhang Q. Chaetospirolactone reverses the apoptotic resistance towards TRAIL in pancreatic cancer. *Biochem Biophys Res Commun* 2018; **495**: 621-628 [PMID: 29107694 DOI: 10.1016/j.bbrc.2017.10.144]

103 **Ashkenazi A**. Directing cancer cells to self-destruct with pro-apoptotic receptor agonists. *Nat Rev Drug Discov* 2008; **7**: 1001-1012 [PMID: 18989337 DOI: 10.1038/nrd2637]

104 **Chen Y**, Ren B, Yang J, Wang H, Yang G, Xu R, You L, Zhao Y. The role of histone methylation in the development of digestive cancers: a potential direction for cancer management. *Signal Transduct Target Ther* 2020; **5**: 143 [PMID: 32747629 DOI: 10.1038/s41392-020-00252-1]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com