**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 63313

**Manuscript Type:** REVIEW

**Histone methylation in pancreatic cancer and its clinical implications**

Liu XY *et al*. Histone methylation in pancreatic cancer

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**Received:** January 27, 2021

**Revised:** March 12, 2021

**Accepted:**

**Published online:**

**Abstract**

Pancreatic cancer (PC) is an aggressive human cancer. Appropriate methods for the diagnosis and treatment of PC have not been found at the genetic level, thus making epigenetics a promising research path in studies of PC. Histone methylation is one of the most complicated types of epigenetic modifications and has proved crucial in the development of PC. Histone methylation is a reversible process regulated by readers, writers, and erasers. Some writers and erasers can be recognized as potential biomarkers and candidate therapeutic targets in PC because of their unusual expression in PC cells compared with normal pancreatic cells. Based on the impact that writers have on the development of PC, some inhibitors of writers have been developed. However, few inhibitors of erasers have been developed and put to clinical use. Meanwhile, there is not enough research on the reader domains. Therefore, the study of erasers and readers is still a promising area. This review focuses on the regulatory mechanism of histone methylation, and the diagnosis and chemotherapy of PC based on it. The future of epigenetic modification in PC research is also discussed.

**Key Words:** Pancreatic cancer; Epigenetics; Histone modification; Methylation; Demethylation; Clinical application

Liu XY, Guo CH, Xi ZY, Xu XQ, Zhao QY, Li LS, Wang Y. Histone methylation in pancreatic cancer and its clinical implications. *World J Gastroenterol* 2021; In press

**Core Tip:** Pancreatic cancer is a highly lethal malignancy of the digestive tract that is difficult to diagnose and treat. Histone methylation/demethylation equilibrium is altered in carcinogenesis, resulting in changes in chromatin structure and gene expression. Not only are histone methylation writers related to histone methylation erasers but histone methylation is also related to other epigenetic modifications. Therefore, histone methylation is addressed as a potentially important chemotherapy drug target.

**INTRODUCTION**

Pancreatic cancer (PC) is a malignant tumor. The lack of adequate diagnostics for PC limits the efficacy of the few currently available treatment options. Current diagnostic methods include clinical biomarkers, imaging, biopsy, *etc.* To date, carcinoembryonic antigen 19 (CA-19) is the only PC clinical biomarker approved by the U.S. Food and Drug Administration[1], but the use of CA-19 is limited by its inadequate sensitivity and specificity[2,3]. Percutaneous biopsy can result in micrometastases in younger patients who receive surgery, so it is only appropriate for inoperable patients[4]. Current diagnostic methods are either inaccurate or limited. Conventional treatment methods for PC mainly include surgery, adjuvant chemotherapy, drug therapy, and radiation therapy[5]. Surgery remains the most important treatment, followed by adjuvant chemotherapy[5]. At present, only 15% to 20% patients can be surgically treated after diagnosis, and only 20% of the patients survive 5 years after receiving surgery[6,7]. Regarding chemotherapy, gemcitabine and other drugs have proved effective for advanced and metastatic PC, but the development of drug resistance has limited the effectiveness[8]. The survival rate of PC patients has not changed much in the past 40 years[8]. The robust molecular biomarkers need to be developed for diagnosis and targeted therapies.

Cancer development is a complex process involving both genetic and epigenetic changes. Genome instability, regulated by both genetic mutations and epigenetic modifications, contributes to tumor progression[9]. The concept of epigenetics itself is evolving with the increase of our knowledge of the molecular mechanism and regulation of gene expression. It is currently widely acknowledged that epigenetics is the study of alternations in gene expression patterns without changes in DNA sequences[10]. Epigenetic modifications include DNA methylation, histone modification and non-coding RNAs. Epigenetic modifications present a new direction for cancer prevention, clinical diagnosis, and drug development.

Histone modification is one of the most important and complicated epigenetic regulatory mechanisms and is crucial in PC. Histone modification affects chromatin structure, transcription, and DNA repair process[11]. Histone modification takes part in the regulation of chromatin architecture and specific loci regulation by recruiting cell-specific transcription factors and interacting with initiation and elongation factors[12]. Histone modification also regulates the transcription process by influencing RNA processing[12]. In terms of regulating chromatin structure, histone modification affects the higher-order chromatin structure by changing the interactions of histones with DNA, and/or by recruiting chromatin remodeling complexes indirectly[13-15].

Histone modifications include histone acetylation, methylation, phosphorylation, and ubiquitination. Histone methylation plays crucial roles in the development of PC. Therefore, this review focuses on histone methylation and its clinical applications.

**Histone methylation**

Post-translational methylation in histone tails is a reversible dynamic chromatin modification. Methyl is dynamically added by methyltransferases-writers, removed by demethylase-erasers, and interpreted by effector proteins-readers[16]. Readers recognize specific sites and promote the recruitment of transcription factors or chromatin-associated protein complexes and bind to histones to enable the localization of enzymes to specific targets[17].

Histone methylation takes place on the residues of arginine, lysine, and histidine. According to the amino acid residues modified, there are arginine residue methyltransferases and lysine residue methyltransferases[18]. Histone arginine methylation is a universal post-translational modification, and aberrant histone arginine methylation is strongly associated with carcinogenesis and metastasis[19]. Arginine residues may be differentially methylated by different types of protein arginine N-methyltransferases (PRMTs)[19].

The maintenance of the balance between histone methylation and demethylation is fundamental to normal cellular development and function[20,21]. The break of the balance between histone methylation and demethylation results in oncogenesis and progression[21,22]. Corresponding to writers, erasers can be divided into arginine residue demethylases and lysine residue demethylases. However, current research on histone arginine residue demethylases is limited, so we only discuss lysine residue demethylases. Based on their mechanism of action, lysine demethylases (KDMs) are classified into two families: flavin adenine dinucleotide (FAD)-dependent and Fe(II) and 2-oxoglutarate (2OG)-dependent[23-25].

The appropriate localization of histone methyltransferase and histone demethylase is dependent on the readers that can recognize histone modifications[26]. The reader can either be an independent polypeptide or a part of methyltransferase/demethylase[27-31]. Some reader domains such as chromodomain[32,33], Tudor domain[34], tryptophan-aspartic acid 40 (WD40) domain[35,36] and plant homeodomain (PHD) finger[37,38] are well known. These reader domains all have their own specific structure[32-38].

**HISTONE METHYLATION WRITERS IN PC**

Among histone methylation, arginine and lysine methylation are the most widely studied in PC[39]. Histone methylation is performed mainly by two types of writers: PRMTs and lysine methyltransferases (KMTs) (Table 1), with S-adenosyl-L-methionine (SAM) as the methyl donor[40].

***PRMTs***

PRMTs catalyze the transfer of a methyl group from SAM to a guanidino-nitrogen atom[41]. Three types of methylated arginine residues are found in mammalian cells: asymmetric dimethyl-arginine (ADMA), symmetric dimethyl-arginine (SDMA) and monomethyl-arginine (MMA)[41]. Depending on their catalytic activity, PRMTs can be classified in three types[42]. Type I PRMTs are responsible for producing ADMA, whose methyl groups are linked to the same guanidino nitrogen atom. Type II PRMTs add the methyl groups on each of the guanidino nitrogen atom of arginine symmetrically, producing SDMA[42]. PRMT7 is the sole member of type III, exclusively catalyzing the formation of MMA[43]. PRMT1 and PRMT5 function in PC[44,45]. PRMT1 belongs to type I and PRMT5 belongs to type II[42].

**PRMT1:** PRMT1 is the founding member of the PRMT family, and PRMT1 can methylate histone H4 at arginine 3. This modification is associated with transcriptional activation[44]. Upregulation of PRMT1 is found in various cancer types[46-49]. PRMT1 is highly expressed in pancreatic ductal adenocarcinoma (PDAC) cells, and elevated PRMT1 levels predict a poor clinical outcome[44]. PRMT1 promotes PC cell growth *in vitro* and *in vivo*[44]. PRMT1 increases the β-catenin protein level in PC cells[44]. Overactivation of β-catenin signaling promotes the growth, migration, and metastasis of PC cells[50-52]. PRMT1 downregulation inhibits PC cell proliferation and invasion[53]. GLI family zinc finger 1 (Gli1) is a substrate of PRMT1 in PDAC. Methylation of Gli1 at R597 by PRMT1 promotes its transcriptional activity by enhancing the binding of Gli1 to the promoters of its target gene[54]. Interruption of Gli1 methylation attenuates oncogenic functions of Gli1 and sensitizes PDAC cells to gemcitabine treatment[54].

**PRMT5:** PRMT5 is a type II writer, responsible for symmetric demethylation[19,55]. PRMT5 regulates the expression of a wide spectrum of target genes by modifying the chromatin structure or transcriptional machinery[56]. Specifically, PRMT5 can catalyze the methylation of arginine 8 on histone H3 and arginine 3 on histone H4 (H4R3)[57]. High expression of PRMT5 has been observed in various cancers. PRMT5 expression improves cancer cell survival, proliferation, migration and metabolism while inhibiting cancer cell apoptosis[55]. PRMT5 expression is significantly upregulated in PC tissues[56]. PRMT5 promotes tumorigenesis and PC cell proliferation[45]. PRMT5 promotes cell migration, invasion, and the epithelial-mesenchymal transition (EMT) *via* activating EGFR/AKT/β-catenin signaling in PC cells[45]. PRMT5 knockdown reduces glucose intake and lactate levels in PC cells[56]. PRMT5 can inhibit the expression of F-Box and WD repeat domain containing 7 (FBW7)[58,59]. PRMT5 inhibits FBW7 *via* suppression of *FBW7* gene promoter activity and elevation of cMyc stability, leading to tumorigenicity and aerobic glycolysis in PC cells[56]. PRMT5 induces the phosphorylation of epidermal growth factor receptor (EGFR) at Y1068 and Y1172[45]. Then PRMT5 activates phosphorylation of AKT and its downstream GSK3β[45].

***KMTs***

KMTs transfer one, two, or three methyl-groups to histone lysine residues[60]. KMTs are categorized into two protein families based on catalytic domain sequence similarity and structural organization[61]. Two major writers, SMYD3 (KMT3E) and EZH2 (KMT6), are related to PC[62,63]. SMYD3 is a member of SET and MYND-domain family[64]. EZH2 belongs to the polycomb family[61].

**SMYD3:** SMYD3 belongs to the SET and MYND-domain family. SMYD3 can promote the proliferation, migration, and invasion of many types of cancer[64]. SMYD3 is a protooncogene in liver, colon and breast tissue based on its high level of endogenous expression and cancer-related promoter polymorphism[65-70]. SMYD3 is upregulated in PC. SMYD3 is positively associated with caspase-3 and MMP-2 expression in PC tissues[62]. Active Src phosphorylates p300 in the nucleus, and then the complex binds to HMGA2 and SMYD3 genes. Therefore, HMGA2 and SMYD3 are regulated to promote PC cell migration and invasion[71].

**EZH2:** EZH2 is the enzymatic subunit of polycomb repressive complex 2 (PRC2), a complex that methylates lysine 27 of histone H3(H3K27) to promote transcriptional silencing[72]. High expression of EZH2 protein has been associated with several cancers[73-75]. EZH2 is overexpressed in PC[76]. FBW7 interacts with EZH2 and downregulates EZH2 *via* ubiquitination and degradation in PC cells[76]. Downregulation of FBW7 induces high EZH2 protein expression and promotes tumor progression in PC[76]. Long non-coding RNA (lncRNA) *BLACAT1* facilitates proliferation, migration, and aerobic glycolysis of PC cells by repressing *CDKN1C* *via* EZH2-induced histone H3 lysine 27 trimethylation (H3K27me3)[77]. EZH2 regulates the expression of miR-139-5p *via* H3K27me3, and the EZH2/miR-139-5p axis participates in the progression of PC, whereby downregulation of EZH2 and upregulation of miR-139-5p repress the EMT and lymph node metastasis of PC[78]. EZH2 can bind to the promoters of P15 and KLF2 to induce H3K27me3[79]. LncRNA *SNHG15* knockdown inhibits PC cell proliferation and tumorigenesis while inducing cell apoptosis, and the *SNHG15*-mediated oncogenic effect is partly by repressing P15 and KLF2 expression *via* EZH2-induced H3K27me3[79].

**HISTONE METHYLATION ERASERS IN PC**

The demethylation of arginine and lysine in histone tails is the two main forms of histone demethylation. Due to the large gaps in research on arginine demethylation, the main situation of KDMs in PC will be mainly described. KDMs can catalyze monomethyl, dimethyl or trimethyl labeling of histone lysine residues[12]. There is some evidence that occurrence, development, and therapy of PC are all related to KDMs[80,81] (Table 2).

***KDM1***

Flavin-dependent KDMs are a subfamily of amine oxidases that catalyze the selective posttranslational oxidative demethylation of methyl lysine side chains within substrates[82]. Two subtypes of KDMs, KDM1A and KDM1B, are related to PC[83,84]. They are expressed at high levels in PC tissues. To date, the expression patterns and physiological functions of KDM1A/LSD1 in PC have not been fully elucidated. KDM1A and hypoxia inducible factor-1α (HIF1α) are the interaction partners of the homeobox protein PROX1[85,86]. KDM1A acts synergistically with HIF1α in maintaining glycolysis[87]. Compared with KDM1A, KDM1B/LSD2 lacks a "tower domain" and has a zinc finger domain in the N-terminal region, which makes KDM1B endowed with different biochemical properties[24,25,88]. KDM1B is related to many important biological functions, including transcriptional regulation, genome imprinting, somatic cell reprogramming, DNA methylation, and signal transduction[89-92]. The downregulation of KDM1B can inhibit PC cell proliferation and promote PC cell apoptosis *in vitro*[93,94].

***JmjC domain-containing protein family***

JmjC domain-containing(JMJD) protein family is a type of Fe (II) and α-ketoglutarate-dependent dioxygenases. The JMJD protein family now consists of 33 members. There are 18 members with the ability to demethylate H3K4, H3K9, H3K27, H3K36, and H4K20[23,95-108].

**KDM2B:** KDM2B acts on H3K36 demethylation. KDM2B enhances the bypass of primary cell senescence by directly binding to tumor suppressor gene *CDKN2A* sites and demethylating histones, thereby guiding the recruitment of PRC2; thus, it plays an important role in cell cycle progression and senescence[109,110]. KDM2B regulates cell proliferation, migration, and angiogenesis[111-113]. KDM2B plays a crucial role in poorly differentiated PDAC, and there is an interaction between EZH2 and KDM2B[114].

**KDM3A:** KDM3A/JMJD1A, one member of the JMJD1 family, participates in transcriptional regulation by demethylating monomethyl or dimethyl H3K9[115,116]. Since cells are heterogeneous in early PDAC tissues, new progress has been made in the study of PDAC morphology, which is specifically manifested by the upregulation of *DCLK1* expression[117]. KDM3A plays a key role in the upregulation of *DCLK1* expression, and KDM3A expression inhibitors can inhibit the malignant properties of PDAC[118].

**KDM4:** TheKDM4 subfamily consists of 12 demethylases including KDM4A, B, C, and D, which can catalyze the removal of inhibitory trimethyl marker of H3K9 and H3K36 related to transcription[98,119]. KDM4A, B, and D play a role in PC mainly. The interaction between regulatory factor X-associated protein RFXAP and KDM4A can disrupt DNA damage repair[120]. RFAXP is a key transcription factor for MHC II molecules[121,122]. It can bind to the promoter of *KDM4A* and induce its expression[120]. In PC, Fisetin can interact with RFXAP/KDM4A to inhibit PC tumor growth *in vivo* and cell proliferation *in vitro*[120]. In PC, KDM4B shows the ability to downregulate E-cadherin[123]. The high nuclear expression of KDM4D in the samples of pancreatic resection margins significantly and independently predicts an earlier recurrence in PC patients[124].

**KDM5:** KDM5 subfamily consists of four members, KDM5A, KDM5B, KDM5C, and KDM5D[125]. The role of KDM5 family in PC is not completely clear. KDM5A is associated with the development of PC[126]. KDM5A inhibits the expression of mitochondrial pyruvate carrier-1 (MPC-1) and controls the metabolites of pyruvate in mitochondria in PDAC[126]. Upregulation of MPC-1 seems to inhibit the development of cancer. Therefore, it can be inferred that KDM5A promotes the development of PDAC.

**KDM6:** KDM6 subfamily is mainly composed of KDM6A/UTX, its paralogs UTY and KDM6B[127]. They can demethylate the dimethyl and trimethyl groups of H3K27. They play important roles in the occurrence and development of many cancers. KDM6A/UTX has been the most frequently mutated epigenetic regulator in cancers including PC[128-133]. In addition, KDM6A also antagonizes PRC2-mediated H3K27 trimethylation catalyzed by EZH2, thereby regulating development[99,104,134]. KDM6A has not been found to function in PC tissues. Downregulation of KDM6B is widespread in many cancer cells[135,136]. Almost all pancreatic epithelial tissues have been detected *KRAS* gene mutations before they become cancerous[137]. KDM6B, which is located downstream of the *KRAS* gene, is upregulated in the pre-tumor phase of pancreatic intraepithelial tumors[138]. It is worth noting that the expression of KDM6B decreases with cancer development.

**KDM7 (PHF and ZF protein subfamily):** At present, the effect of KDM7 subfamily on PC has been seldom developed. According to relevant data, KDM7A may be related to the occurrence and development of PC[139].

**READER DOMAIN IN WRITERS AND ERASERS**

PHD fingers are central “readers” of histone post-translational modifications. They recognize specific histone modifications and bind to histone to ensure the different enzymes to locate in special targets[140,141]. They are structurally conserved, represented by the canonical C4HC2C/H sequence coordinating two zinc ions. They present in many chromatin-modifying proteins, such as demethylases or methyltransferases), or act as scaffolding proteins that can connect multi-subunit enzymatic complexes with a particular genomic region[30,140,141]. In this part, we will discuss how PHD fingers regulate histone methylation/demethylation and their binding substrates (Table 3).

***Regulation of writers by PHD finger***

KMT2A-E all have PHD fingers, but the number of PHD fingers in these proteins is different. KMT2A and KMT2B have four PHD fingers, while KMT2C has eight PHD fingers and KMT2D has seven PHD fingers, but KMT2E only has one PHD finger. There are 24 PHD fingers in KMT2A-E[142].

**Regulation of KMT2A and KMT2B by PHD finger:** KMT2A and KMT2B have similar domain architecture and both contain three consecutive PHD fingers, PHD1-3. These consecutive PHD fingers are followed by a bromodomain and the fourth PHD4 finger[142]. The precise function of PHD1 finger in KMT2A and KMT2B is unclear, but it can regulate the intramolecular interactions between N-terminal and C-terminal segments[143]. PHD1 fingers are necessary for holocomplex formation and are implicated in tumor suppression[143]. PHD2 finger has an E3 ubiquitin ligase in the presence of the E2-conjugating enzyme CDC34[144]. Mutation of the PHD2 finger will cause increased transactivation ability of KMT2A and its recruitment to target genes[142], because of increased protein stability[144]. PHD3 finger binds to H3K4me3/me2, but the affinity between PHD3 finger and H3K4me2 is eight times lower than the affinity between PHD3 finger and H3K4me3[145]. Although PHD3 finger can recognize H3K4me3, the special function of KMT2A in transcriptional maintenance is unclear[145]. One possibility is that binding of H3K4me3 by PHD3 finger is necessary for the transcription-promoting effects of KMT2A, and another possibility is that newly deposited H3K4me3 mark helps KMT2A slide along the gene to set a broad, methylated chromatin domain[145]. The stability of KMT2A is dependent on its intramolecular interaction which is mediated *via* its PHD1 finger with PHD4 finger and the phenylalanine/tyrosine-rich domain of KMT2A[143]. Therefore, PHD4 finger in KMT2A can improve the stability of KMT2A in case of hydrolysis.

**Regulation of KMT2C by PHD finger:** KMT2C contains eight PHD fingers while KMT2D contains seven PHD fingers[142]. Although the function of PHD fingers in KMT2C is unclear, the functional extended PHD finger is important for KMT2C to be recruited to its target genes[146]. PHD4, PHD5, and PHD6 in KMT2D are tandem and these tandem PHDs can bind to unmethylated or asymmetrically demethylated H4 arginine3[147]. This connection is important for nucleosomal methylation activity and mediates stem cell differentiation by KMT2D[147]. But this binding ability is repressed by symmetrical demethylation on arginine-3 of histone H4 (H4R3me2s), because H4R3me2s can hinder the histone binding ability and catalytic activity in PHD4-6[142,147].

**Regulation of KMT2E by PHD finger:** The binding of KMT2E and histone is based on its single PHD finger which can bind to H3K4me3, and this special spatial structure of KMT2E makes it possible to recognize H3K4me3[148]. Although KMT2E can also bind to H3K4me2 and H3K4me1, the stability of binding of H3K4me2 and KMT2E is five times weaker than H3K4me3, while the stability of binding of H3K4me1 and KMT2E is sixteen times weaker than H3K4me3[148]. This can facilitate the recruitment of KMT2E to active transcription chromatin regions[148,149].

***Regulation of erasers by PHD finger***

PHD fingers can be found in KDMs[150,151]. These PHD fingers bind to the tail of H3 to enable the localization of enzymes to specific targets[152], and promote the recruitment of transcription factors or chromatin-associated protein complexes[17].

**Regulation of KDM4 subfamily by PHD finger:** PHD fingers can be found in KDM4 subfamily. KDM4A, KDM4B, and KDM4C have a catalytic histone demethylase domain, double PHD and Tudor domains, whereas KDM4D contains only a catalytic domain and lacks PHD and Tudor domains[153,154]. Although KDM4A-C have PHD fingers, the function of PHD fingers is unclear[155].

**Regulation of KDM5 subfamily by PHD finger:** KDM5 subfamily, including KDM5A-D, catalyze demethylation of the transcriptionally activating trimethylated and demethylated lysine-4 mark on H3[100,103,156,157]. KDM5A contains three PHD fingers (PHD1, PHD2, PHD3). Qualitative pull-down assays with isolated PHD1 domain of KDM5A show that it binds to unmodified H3K4 peptide[158]. The PHD1 finger preferentially recognizes unmethylated H3K4 histone tail, which is a KDM5A-mediated trimethylation products of H3K4 (H3K4me3) demethylation[151]. The function of PHD2 finger is unknown. PHD3 finger has been studied in the context of its fusion with nucleoporin NUP98 and it specifically binds to the H3K4me3, with a decrease in affinity for lower methylation states[17,158]. Since these preferred binding substrates are the products of KDM5A-mediated demethylation, a model in which demethylation can propagate along nucleosomes *via* a positive-feedback regulatory mechanism, has been put forward[151].

The KDM5B PHD1 finger can recognize the N-terminus of H3, which is unmodified or methylated at Lys9[17]. The KDM5B PHD2 finger cannot bind to histone. The KDM5B PHD3 finger prefers to bind to H3K4me3[17]. The PHD1 finger specifically binds to H3K4me0, and the PHD3 finger is selective for H3K4me3. A combination of two ‘readers’ capable of recognizing distinctive epigenetic marks is likely to impact KDM5B activity. Binding of PHD1 to H3K4me0 may provide an anchoring mechanism for KDM5B to sense H3K4me3 through PHD3 and slide along the H3K4me3-enriched promoters, demethylating nearby methylated H3K4 and further spreading the transcriptionally inactive state of chromatin[17]. In addition, abrogation of H3 tail recognition by point mutation in the PHD1 domain of KDM5B decreases H3K4 demethylation in cells, resulting in the repression of tumor suppressor genes[159]. Therefore, the importance of interaction between PHD1 and H3 tail is proved.

Similarly, the PHD1 finger domain in KDM5C is close to the JmjC domain, and the linker of JmjC domain is 13 amino acids long and is expected to recognize and bind to H3K9me3[157,160]. Although the PHD1 domain is not necessary for the demethylase activity, it helps to recognize the substrate peptide[157,161]. The interaction between PHD1 domain and JmjC domain stabilizes the substrate peptide and the PHD1 domain can help precisely position H3K4 in the JmjC domain[162].

**Regulation of KDM7 by PHD finger:** PHF8 belongs to KDM7 subfamily and transcriptionally removes suppressive demethylation and monomethylation of lysine 9 and 27 on H3 and lysine 20 on H4[163]. PHF8 has a PHD finger which is closed to the catalytic domain. PHD finger in PHF8 plays a significant role in PHF8 substrate recognition, because it helps to improve substrate affinity and specificity[164]. PHF8 can be recruited to the promoters through the combination of its PHD finger and H3K4me2/3 during the cell cycle transition from G1 to S[107]. Although the functions of PHD fingers can be found in gastric cancer[165], breast cancer[166], colorectal cancer[167], lung cancer[168], *etc.*, the functions of PHD finger are still unclear in PC.

**Clinical application**

Epigenetic genes play vital roles in maintaining structural stability and physiological functions of normal chromosomes and are deficient in some patients with PC, thereby serving as potential targets for correcting these deficiencies and precisely killing these aberrant PC cells[169]. The discovery of histone methyltransferases, demethylases and their active sites has provided new insights in the diagnosis and treatment of PC. The active sites and mechanism of the inhibitors in PC treatment are shown in Table 4.

Histone modifications define the previously unrecognized subsets of PC patients with different epigenetic states and therefore represent the prognostic and predictive biomarkers that can be used to guide clinical decisions, such as the use of fluorouracil chemotherapy[170]. H3K4me2, H3K9me2, or H3K18AC expressed at low levels are positively correlated with the poor prognosis of PC[170]. EZH2 expression is higher in PC cells than in normal cells; thus, EZH2 can be used as a potential biomarker for early diagnosis of PDAC[171]. High expression of KDM4D in benign cells near the edge of surgically resected PC tissues is predictive of early recurrence[124]. The discovery of epigenetic biomarkers can provide a great reference for early diagnosis, drug selection and surgery prognosis of PC.

SMYD3 is a candidate therapeutic target against PC, lung cancer and potentially other RAS-driven tumors[172]. In mice, complete loss of SMYD3 function with no apparent phenotype suggests that SMYD3 inhibitors, as chemotherapeutic agents, cause minimal collateral toxicity. The clinically used combination of Raf protein kinase or dual specificity threonine/tyrosine kinase inhibitors and SMYD3 inhibitors can reduce drug toxicity and suppress the development of drug resistance[172].

SMYD3 inhibitor piperidine-4-formamide-acetanilide compound, BCI-121, is a small molecule inhibitor that significantly inhibits proliferation in PC cell lines with high expression of SMYD3. BCI-121 and histone competitively bind to SMYD3; BCI-121 binds inside the lysine channel, which connects cofactor binding sites and histone peptide binding sites[173].

The PRMT5 inhibitor EZP015556 targets *MTAP* (a gene commonly lost in PC) negative tumors, which indicates that it is an effective treatment for a subpopulation of *MTAP* positive tumors. According to the individualized medication approach, the therapeutic response in different patient-derived organoids (PDOs), developed directly from patient tumor tissue is different. The PDO model is used to validate the effectiveness of PMRT5 inhibition as a potential treatment for PDAC[174]. EZH2 expression in PC cells is significantly higher than that in normal pancreatic duct cells and fibroblasts. 3-Deazaneplanocin A (DZNeP) regulates the expression of EZH2 and H3K27me3, synergically enhancing the anti-proliferative activity of gemcitabine and significantly increasing the apoptosis rate of cells[175]. DZNeP is an S-adenosine homocysteine hydrolase inhibitor. DZNeP also enhances the mRNA and protein expression of nucleoside transporter HENT1/HCNT1[175]. The combination of DZNeP and DZNeP/gemcitabine significantly reduces the growth volume of PDAC spheres in selective medium[175].

Bromodomain and extra-terminal (BET) inhibitors and EZH2 inhibitors are designed to rescue the dysregulated KMT2C/MLL3-KDM6A/UTX-PRC2 regulatory axis and have achieved preliminary success in preclinical models. The regulatory axis regulates the expression of various downstream tumor suppressor genes[169]. Therefore, rebalancing this axis represents a new approach to PDAC therapy.

Defects in KDM6A make sex-specific squamous PC sensitive to bromouracil and BET inhibitors[169]. BET inhibitor JQ1 reverses squamous cell differentiation and inhibits tumor growth *in vivo* by decreasing MYC pathway activity and p63 levels[176]. JQ1 affects cancer-associated fibroblast (CAF) activation by acting on the Hedgehog and TGF-β pathways. JQ1 inhibitor converts α-SMA-positive CAFs to α-SMA-negative CAFs, but does not eliminate CAFs[177].

Small molecules containing 8-hydroxyquinoline structure are competitive inhibitors of KDM4 (also known as JMJD2) family, binding active iron to inhibit the activity of KDM4 and regulate demethylation of H3K9 sites[178]. KDM4C inhibitor SD70 can inhibit the growth of prostate cancer cells[179].

Many types of inhibitors of KDM1A have been reported, but the inhibitors of this enzyme are mainly targeted at acute myeloid leukemia or small cell lung cancer, *etc.* And there are few studies on PC. For example, SP2509 is a noncompetitive inhibitor, and is used in current clinical trials for the treatment of acute myeloid leukemia or small cell lung cancer[180]. Ory-1001 effectively inactivates LSD1 and is highly selective for FAD-dependent ammonia oxidase[181]. The application of histone demethylase inhibitors in the treatment of PC is still limited, so it is necessary to strengthen the exploration of the treatment of PC based on the existing research.

**Future directions**

Histone writers and erasers do not work independently. In fact, the interactions between writers and erasers include the positive correlativity between EZH2 and KDM2B, and the synergistic effects of EZH2 and KDM6A[182,183]. In bladder cancer, the H3K27 demethylase KDM6A gene often has mutations[131,184]. This makes cancer tissues that have lost KDM6A more vulnerable to EZH2 attack[185]. This accelerates the onset of tumors. The expression of EZH2 and KDM2B in ovarian cancer is positively correlated[183]. Therefore, knocking down the KDM2B gene is beneficial to inhibit the migration of ovarian cancer cells *in vitro*.

Many problems remain in the research of histone modifications. Research on histone methyltransferases is relatively adequate, but there are few articles about the mechanism of SMYD2, so SMYD2 is not mentioned in our review. Current research on histone arginine residue demethylases has not yet fully achieved results. Therefore, only histone lysine residue demethylases are discussed. However, the effect of KDM7 subfamily demethylases on PC has seldom been proved, so only some guesses about the effect of KDM7A are mentioned. Besides, the study of the interactions between writers and erasers in PC is still in a blank state. The role of the reader domain in PC remains unclear. This review only lists the roles of the PHD domain in the localization of histone modifications and the recruitment of related protein complexes. Reader domain is still a potential research direction in PC.

The study of histone methylation and demethylation has enlightening effects on the diagnosis, treatment, and prognosis of PC. Histone modifications can be used to predict in the prognosis of PC patients[171]. Histone methyltransferase and demethylase inhibitors are used clinically to treat PC. The corresponding inhibitors act on the signal regulatory pathway and change the signal expression of downstream target cells, thus regulating the growth and development of cancer cells. At present, the research of histone demethylase inhibitors is inadequate. Therefore, histone demethylase inhibitors need to be further explored.

The effect of histone modifications on PC is interdependent. The interactions between histone modifications and other epigenetic forms can influence the occurrence and progression of cancers such as cervical cancer and breast cancer. The effect of these interactions enlightens the research on PC. DNA methylation and the expression of miRNAs can be regulated by histone methyltransferases and demethylases, thereby causing alternations of developing process of cancer. Histone methyltransferase EZH2 epigenetically silences tumor-suppressor miRNAs, such as miR-139-5p, miR-125b, miR-101, let-7c and miR-200b, thereby promoting cancer cell metastasis[186]. Histone demethylase KDM5B targets H3K4 demethylation of miR-let-7e and promotes tumor cell proliferation through epigenetically inhibiting the tumor suppressor miR[187]. The combination of EZH2 and promoter region induces the expression of specific target protein H3K27me3, thereby reducing the expression of downstream gene, DNA (cytosine-5)-methyltransferase 3A (DNMT3A)[10]. EZH2-H3K27me3-DNMT3A is the key factor of regulating cervical total stimulus molecule Tim-3/galectin-9, which results in immune escape in the process of malignant transformation[10]. It is reasonable to speculate that the interaction between histone methylation and other epigenetic modifications may also play a role in PC. This opinion draws some inspiration and reference to future research of PC.

**CONCLUSION**

This review focuses on the mechanism of histone methylation in PC. Histone methylation is mainly regulated by writer, reader and eraser. Writer refers to histone methyltransferase, eraser refers to histone demethylase and reader refers to the modification domain of histone methyltransferase and demethylase. Reader can be an independent polypeptide or a component of methyltransferase and demethylase. On the one hand, histone methyltransferase can promote the proliferation and invasion of PC cells. On the other hand, histone methyltransferase can inhibit the proliferation of cancer cells. Histone demethylase promotes the occurrence of PC and is related to apoptosis. Reader domain plays a role in guiding related methyltransferases and demethylases to identify corresponding sites during the methylation and demethylation process.

**REFERENCES**

1 **Daoud AZ**, Mulholland EJ, Cole G, McCarthy HO. MicroRNAs in Pancreatic Cancer: biomarkers, prognostic, and therapeutic modulators. *BMC Cancer* 2019; **19**: 1130 [PMID: 31752758 DOI: 10.1186/s12885-019-6284-y]

2 **Duffy MJ**, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, Nicolini A, Topolcan O, Heinemann V. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. *Ann Oncol* 2010; **21**: 441-447 [PMID: 19690057 DOI: 10.1093/annonc/mdp332]

3 **Ansari D**, Torén W, Zhou Q, Hu D, Andersson R. Proteomic and genomic profiling of pancreatic cancer. *Cell Biol Toxicol* 2019; **35**: 333-343 [PMID: 30771135 DOI: 10.1007/s10565-019-09465-9]

4 **Goral V**. Pancreatic Cancer: Pathogenesis and Diagnosis. *Asian Pac J Cancer Prev* 2015; **16**: 5619-5624 [PMID: 26320426 DOI: 10.7314/apjcp.2015.16.14.5619]

5 **Dumont R**, Puleo F, Collignon J, Meurisse N, Chavez M, Seidel L, Gast P, Polus M, Loly C, Delvenne P, Meunier P, Hustinx R, Deroover A, Detry O, Louis E, Martinive P, Van Daele D. A single center experience in resectable pancreatic ductal adenocarcinoma : the limitations of the surgery-first approach. Critical review of the literature and proposals for practice update. *Acta Gastroenterol Belg* 2017; **80**: 451-461 [PMID: 29560639]

6 **Puckett Y**, Garfield K. Pancreatic Cancer 2021 [PMID: 30085538]

7 **Labori KJ**, Katz MH, Tzeng CW, Bjørnbeth BA, Cvancarova M, Edwin B, Kure EH, Eide TJ, Dueland S, Buanes T, Gladhaug IP. Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma - A population-based cohort study. *Acta Oncol* 2016; **55**: 265-277 [PMID: 26213211 DOI: 10.3109/0284186X.2015.1068445]

8 **Zeng S**, Pöttler M, Lan B, Grützmann R, Pilarsky C, Yang H. Chemoresistance in Pancreatic Cancer. *Int J Mol Sci* 2019; **20** [PMID: 31514451 DOI: 10.3390/ijms20184504]

9 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

10 **Zhang L**, Tian S, Pei M, Zhao M, Wang L, Jiang Y, Yang T, Zhao J, Song L, Yang X. Crosstalk between histone modification and DNA methylation orchestrates the epigenetic regulation of the costimulatory factors, Tim‑3 and galectin‑9, in cervical cancer. *Oncol Rep* 2019; **42**: 2655-2669 [PMID: 31661141 DOI: 10.3892/or.2019.7388]

11 **Ning B**, Li W, Zhao W, Wang R. Targeting epigenetic regulations in cancer. *Acta Biochim Biophys Sin (Shanghai)* 2016; **48**: 97-109 [PMID: 26508480 DOI: 10.1093/abbs/gmv116]

12 **Greer EL**, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. *Nat Rev Genet* 2012; **13**: 343-357 [PMID: 22473383 DOI: 10.1038/nrg3173]

13 **Suganuma T**, Workman JL. Signals and combinatorial functions of histone modifications. *Annu Rev Biochem* 2011; **80**: 473-499 [PMID: 21529160 DOI: 10.1146/annurev-biochem-061809-175347]

14 **Bell O**, Tiwari VK, Thomä NH, Schübeler D. Determinants and dynamics of genome accessibility. *Nat Rev Genet* 2011; **12**: 554-564 [PMID: 21747402 DOI: 10.1038/nrg3017]

15 **de Almeida SF**, Grosso AR, Koch F, Fenouil R, Carvalho S, Andrade J, Levezinho H, Gut M, Eick D, Gut I, Andrau JC, Ferrier P, Carmo-Fonseca M. Splicing enhances recruitment of methyltransferase HYPB/Setd2 and methylation of histone H3 Lys36. *Nat Struct Mol Biol* 2011; **18**: 977-983 [PMID: 21792193 DOI: 10.1038/nsmb.2123]

16 **Hyun K**, Jeon J, Park K, Kim J. Writing, erasing and reading histone lysine methylations. *Exp Mol Med* 2017; **49**: e324 [PMID: 28450737 DOI: 10.1038/emm.2017.11]

17 **Klein BJ**, Piao L, Xi Y, Rincon-Arano H, Rothbart SB, Peng D, Wen H, Larson C, Zhang X, Zheng X, Cortazar MA, Peña PV, Mangan A, Bentley DL, Strahl BD, Groudine M, Li W, Shi X, Kutateladze TG. The histone-H3K4-specific demethylase KDM5B binds to its substrate and product through distinct PHD fingers. *Cell Rep* 2014; **6**: 325-335 [PMID: 24412361 DOI: 10.1016/j.celrep.2013.12.021]

18 **Varier RA**, Timmers HT. Histone lysine methylation and demethylation pathways in cancer. *Biochim Biophys Acta* 2011; **1815**: 75-89 [PMID: 20951770 DOI: 10.1016/j.bbcan.2010.10.002]

19 **Zhang J**, Jing L, Li M, He L, Guo Z. Regulation of histone arginine methylation/demethylation by methylase and demethylase (Review). *Mol Med Rep* 2019; **19**: 3963-3971 [PMID: 30942418 DOI: 10.3892/mmr.2019.10111]

20 **McCabe MT**, Mohammad HP, Barbash O, Kruger RG. Targeting Histone Methylation in Cancer. *Cancer J* 2017; **23**: 292-301 [PMID: 28926430 DOI: 10.1097/PPO.0000000000000283]

21 **Chi P**, Allis CD, Wang GG. Covalent histone modifications--miswritten, misinterpreted and mis-erased in human cancers. *Nat Rev Cancer* 2010; **10**: 457-469 [PMID: 20574448 DOI: 10.1038/nrc2876]

22 **Shi Y**, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, Casero RA, Shi Y. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* 2004; **119**: 941-953 [PMID: 15620353 DOI: 10.1016/j.cell.2004.12.012]

23 **Tsukada Y**, Fang J, Erdjument-Bromage H, Warren ME, Borchers CH, Tempst P, Zhang Y. Histone demethylation by a family of JmjC domain-containing proteins. *Nature* 2006; **439**: 811-816 [PMID: 16362057 DOI: 10.1038/nature04433]

24 **Karytinos A**, Forneris F, Profumo A, Ciossani G, Battaglioli E, Binda C, Mattevi A. A novel mammalian flavin-dependent histone demethylase. *J Biol Chem* 2009; **284**: 17775-17782 [PMID: 19407342 DOI: 10.1074/jbc.M109.003087]

25 **Fang R**, Barbera AJ, Xu Y, Rutenberg M, Leonor T, Bi Q, Lan F, Mei P, Yuan GC, Lian C, Peng J, Cheng D, Sui G, Kaiser UB, Shi Y, Shi YG. Human LSD2/KDM1b/AOF1 regulates gene transcription by modulating intragenic H3K4me2 methylation. *Mol Cell* 2010; **39**: 222-233 [PMID: 20670891 DOI: 10.1016/j.molcel.2010.07.008]

26 **Torres IO**, Fujimori DG. Functional coupling between writers, erasers and readers of histone and DNA methylation. *Curr Opin Struct Biol* 2015; **35**: 68-75 [PMID: 26496625 DOI: 10.1016/j.sbi.2015.09.007]

27 **Musselman CA**, Khorasanizadeh S, Kutateladze TG. Towards understanding methyllysine readout. *Biochim Biophys Acta* 2014; **1839**: 686-693 [PMID: 24727128 DOI: 10.1016/j.bbagrm.2014.04.001]

28 **Upadhyay AK**, Horton JR, Zhang X, Cheng X. Coordinated methyl-lysine erasure: structural and functional linkage of a Jumonji demethylase domain and a reader domain. *Curr Opin Struct Biol* 2011; **21**: 750-760 [PMID: 21872465 DOI: 10.1016/j.sbi.2011.08.003]

29 **Verrier L**, Vandromme M, Trouche D. Histone demethylases in chromatin cross-talks. *Biol Cell* 2011; **103**: 381-401 [PMID: 21736555 DOI: 10.1042/BC20110028]

30 **Musselman CA**, Kutateladze TG. Handpicking epigenetic marks with PHD fingers. *Nucleic Acids Res* 2011; **39**: 9061-9071 [PMID: 21813457 DOI: 10.1093/nar/gkr613]

31 **Lalonde ME**, Cheng X, Côté J. Histone target selection within chromatin: an exemplary case of teamwork. *Genes Dev* 2014; **28**: 1029-1041 [PMID: 24831698 DOI: 10.1101/gad.236331.113]

32 **Hard R**, Li N, He W, Ross B, Mo GCH, Peng Q, Stein RSL, Komives E, Wang Y, Zhang J, Wang W. Deciphering and engineering chromodomain-methyllysine peptide recognition. *Sci Adv* 2018; **4**: eaau1447 [PMID: 30417094 DOI: 10.1126/sciadv.aau1447]

33 **Yap KL**, Zhou MM. Structure and mechanisms of lysine methylation recognition by the chromodomain in gene transcription. *Biochemistry* 2011; **50**: 1966-1980 [PMID: 21288002 DOI: 10.1021/bi101885m]

34 **El Agha E**, Kramann R, Schneider RK, Li X, Seeger W, Humphreys BD, Bellusci S. Mesenchymal Stem Cells in Fibrotic Disease. *Cell Stem Cell* 2017; **21**: 166-177 [PMID: 28777943 DOI: 10.1016/j.stem.2017.07.011]

35 **Bergamin E**, Blais A, Couture JF. Keeping them all together: β-propeller domains in histone methyltransferase complexes. *J Mol Biol* 2014; **426**: 3363-3375 [PMID: 24853063 DOI: 10.1016/j.jmb.2014.05.010]

36 **Xu C**, Min J. Structure and function of WD40 domain proteins. *Protein Cell* 2011; **2**: 202-214 [PMID: 21468892 DOI: 10.1007/s13238-011-1018-1]

37 **Adams-Cioaba MA**, Min J. Structure and function of histone methylation binding proteins. *Biochem Cell Biol* 2009; **87**: 93-105 [PMID: 19234526 DOI: 10.1139/O08-129]

38 **Liu R**, Gao J, Yang Y, Qiu R, Zheng Y, Huang W, Zeng Y, Hou Y, Wang S, Leng S, Feng D, Yu W, Sun G, Shi H, Teng X, Wang Y. PHD finger protein 1 (PHF1) is a novel reader for histone H4R3 symmetric dimethylation and coordinates with PRMT5-WDR77/CRL4B complex to promote tumorigenesis. *Nucleic Acids Res* 2018; **46**: 6608-6626 [PMID: 29846670 DOI: 10.1093/nar/gky461]

39 **Ma F**, Zhang CY. Histone modifying enzymes: novel disease biomarkers and assay development. *Expert Rev Mol Diagn* 2016; **16**: 297-306 [PMID: 26750583 DOI: 10.1586/14737159.2016.1135057]

40 **Morera L**, Lübbert M, Jung M. Targeting histone methyltransferases and demethylases in clinical trials for cancer therapy. *Clin Epigenetics* 2016; **8**: 57 [PMID: 27222667 DOI: 10.1186/s13148-016-0223-4]

41 **Poulard C**, Corbo L, Le Romancer M. Protein arginine methylation/demethylation and cancer. *Oncotarget* 2016; **7**: 67532-67550 [PMID: 27556302 DOI: 10.18632/oncotarget.11376]

42 **Rakow S**, Pullamsetti SS, Bauer UM, Bouchard C. Assaying epigenome functions of PRMTs and their substrates. *Methods* 2020; **175**: 53-65 [PMID: 31542509 DOI: 10.1016/j.ymeth.2019.09.014]

43 **Zurita-Lopez CI**, Sandberg T, Kelly R, Clarke SG. Human protein arginine methyltransferase 7 (PRMT7) is a type III enzyme forming ω-NG-monomethylated arginine residues. *J Biol Chem* 2012; **287**: 7859-7870 [PMID: 22241471 DOI: 10.1074/jbc.M111.336271]

44 **Song C**, Chen T, He L, Ma N, Li JA, Rong YF, Fang Y, Liu M, Xie D, Lou W. PRMT1 promotes pancreatic cancer growth and predicts poor prognosis. *Cell Oncol (Dordr)* 2020; **43**: 51-62 [PMID: 31520395 DOI: 10.1007/s13402-019-00435-1]

45 **Ge L**, Wang H, Xu X, Zhou Z, He J, Peng W, Du F, Zhang Y, Gong A, Xu M. PRMT5 promotes epithelial-mesenchymal transition *via* EGFR-β-catenin axis in pancreatic cancer cells. *J Cell Mol Med* 2020; **24**: 1969-1979 [PMID: 31851779 DOI: 10.1111/jcmm.14894]

46 **Choucair A**, Pham TH, Omarjee S, Jacquemetton J, Kassem L, Trédan O, Rambaud J, Marangoni E, Corbo L, Treilleux I, Le Romancer M. The arginine methyltransferase PRMT1 regulates IGF-1 signaling in breast cancer. *Oncogene* 2019; **38**: 4015-4027 [PMID: 30692633 DOI: 10.1038/s41388-019-0694-9]

47 **Li Z**, Wang D, Lu J, Huang B, Wang Y, Dong M, Fan D, Li H, Gao Y, Hou P, Li M, Liu H, Pan ZQ, Zheng J, Bai J. Methylation of EZH2 by PRMT1 regulates its stability and promotes breast cancer metastasis. *Cell Death Differ* 2020; **27**: 3226-3242 [PMID: 32895488 DOI: 10.1038/s41418-020-00615-9]

48 **He L**, Hu Z, Sun Y, Zhang M, Zhu H, Jiang L, Zhang Q, Mu D, Zhang J, Gu L, Yang Y, Pan FY, Jia S, Guo Z. PRMT1 is critical to FEN1 expression and drug resistance in lung cancer cells. *DNA Repair (Amst)* 2020; **95**: 102953 [PMID: 32861926 DOI: 10.1016/j.dnarep.2020.102953]

49 **Li M**, An W, Xu L, Lin Y, Su L, Liu X. The arginine methyltransferase PRMT5 and PRMT1 distinctly regulate the degradation of anti-apoptotic protein CFLARL in human lung cancer cells. *J Exp Clin Cancer Res* 2019; **38**: 64 [PMID: 30736843 DOI: 10.1186/s13046-019-1064-8]

50 **Yu L**, Li X, Li H, Chen H, Liu H. Rab11a sustains GSK3β/Wnt/β-catenin signaling to enhance cancer progression in pancreatic cancer. *Tumour Biol* 2016; **37**: 13821-13829 [PMID: 27481517 DOI: 10.1007/s13277-016-5172-1]

51 **Ji M**, Fan D, Yuan L, Zhang Y, Dong W, Peng X. EBP50 inhibits pancreatic cancer cell growth and invasion by targeting the β-catenin/E-cadherin pathway. *Exp Ther Med* 2015; **10**: 1311-1316 [PMID: 26622484 DOI: 10.3892/etm.2015.2684]

52 **Zhou W**, Li Y, Gou S, Xiong J, Wu H, Wang C, Yan H, Liu T. MiR-744 increases tumorigenicity of pancreatic cancer by activating Wnt/β-catenin pathway. *Oncotarget* 2015; **6**: 37557-37569 [PMID: 26485754 DOI: 10.18632/oncotarget.5317]

53 **Lin Z**, Chen Y, Lin Z, Chen C, Dong Y. Overexpressing PRMT1 Inhibits Proliferation and Invasion in Pancreatic Cancer by Inverse Correlation of ZEB1. *IUBMB Life* 2018; **70**: 1032-1039 [PMID: 30194893 DOI: 10.1002/iub.1917]

54 **Wang Y**, Hsu JM, Kang Y, Wei Y, Lee PC, Chang SJ, Hsu YH, Hsu JL, Wang HL, Chang WC, Li CW, Liao HW, Chang SS, Xia W, Ko HW, Chou CK, Fleming JB, Wang H, Hwang RF, Chen Y, Qin J, Hung MC. Oncogenic Functions of Gli1 in Pancreatic Adenocarcinoma Are Supported by Its PRMT1-Mediated Methylation. *Cancer Res* 2016; **76**: 7049-7058 [PMID: 27758883 DOI: 10.1158/0008-5472.Can-16-0715]

55 **Yuan Y**, Nie H. Protein arginine methyltransferase 5: a potential cancer therapeutic target. *Cell Oncol (Dordr)* 2021; **44**: 33-44 [PMID: 33469838 DOI: 10.1007/s13402-020-00577-7]

56 **Qin Y**, Hu Q, Xu J, Ji S, Dai W, Liu W, Xu W, Sun Q, Zhang Z, Ni Q, Zhang B, Yu X, Xu X. PRMT5 enhances tumorigenicity and glycolysis in pancreatic cancer *via* the FBW7/cMyc axis. *Cell Commun Signal* 2019; **17**: 30 [PMID: 30922330 DOI: 10.1186/s12964-019-0344-4]

57 **Kim H**, Ronai ZA. PRMT5 function and targeting in cancer. *Cell Stress* 2020; **4**: 199-215 [PMID: 32743345 DOI: 10.15698/cst2020.08.228]

58 **Davis RJ**, Welcker M, Clurman BE. Tumor suppression by the Fbw7 ubiquitin ligase: mechanisms and opportunities. *Cancer Cell* 2014; **26**: 455-464 [PMID: 25314076 DOI: 10.1016/j.ccell.2014.09.013]

59 **Shimizu K**, Nihira NT, Inuzuka H, Wei W. Physiological functions of FBW7 in cancer and metabolism. *Cell Signal* 2018; **46**: 15-22 [PMID: 29474981 DOI: 10.1016/j.cellsig.2018.02.009]

60 **Black JC**, Van Rechem C, Whetstine JR. Histone lysine methylation dynamics: establishment, regulation, and biological impact. *Mol Cell* 2012; **48**: 491-507 [PMID: 23200123 DOI: 10.1016/j.molcel.2012.11.006]

61 **McGrath J**, Trojer P. Targeting histone lysine methylation in cancer. *Pharmacol Ther* 2015; **150**: 1-22 [PMID: 25578037 DOI: 10.1016/j.pharmthera.2015.01.002]

62 **Zhu CL**, Huang Q. Overexpression of the SMYD3 Promotes Proliferation, Migration, and Invasion of Pancreatic Cancer. *Dig Dis Sci* 2020; **65**: 489-499 [PMID: 31441002 DOI: 10.1007/s10620-019-05797-y]

63 **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]

64 **Giakountis A**, Moulos P, Sarris ME, Hatzis P, Talianidis I. Smyd3-associated regulatory pathways in cancer. *Semin Cancer Biol* 2017; **42**: 70-80 [PMID: 27554136 DOI: 10.1016/j.semcancer.2016.08.008]

65 **Foreman KW**, Brown M, Park F, Emtage S, Harriss J, Das C, Zhu L, Crew A, Arnold L, Shaaban S, Tucker P. Structural and functional profiling of the human histone methyltransferase SMYD3. *PLoS One* 2011; **6**: e22290 [PMID: 21779408 DOI: 10.1371/journal.pone.0022290]

66 **Hamamoto R**, Furukawa Y, Morita M, Iimura Y, Silva FP, Li M, Yagyu R, Nakamura Y. SMYD3 encodes a histone methyltransferase involved in the proliferation of cancer cells. *Nat Cell Biol* 2004; **6**: 731-740 [PMID: 15235609 DOI: 10.1038/ncb1151]

67 **Hamamoto R**, Silva FP, Tsuge M, Nishidate T, Katagiri T, Nakamura Y, Furukawa Y. Enhanced SMYD3 expression is essential for the growth of breast cancer cells. *Cancer Sci* 2006; **97**: 113-118 [PMID: 16441421 DOI: 10.1111/j.1349-7006.2006.00146.x]

68 **Silva FP**, Hamamoto R, Kunizaki M, Tsuge M, Nakamura Y, Furukawa Y. Enhanced methyltransferase activity of SMYD3 by the cleavage of its N-terminal region in human cancer cells. *Oncogene* 2008; **27**: 2686-2692 [PMID: 17998933 DOI: 10.1038/sj.onc.1210929]

69 **Tsuge M**, Hamamoto R, Silva FP, Ohnishi Y, Chayama K, Kamatani N, Furukawa Y, Nakamura Y. A variable number of tandem repeats polymorphism in an E2F-1 binding element in the 5' flanking region of SMYD3 is a risk factor for human cancers. *Nat Genet* 2005; **37**: 1104-1107 [PMID: 16155568 DOI: 10.1038/ng1638]

70 **Wang H**, Liu Y, Tan W, Zhang Y, Zhao N, Jiang Y, Lin C, Hao B, Zhao D, Qian J, Lu D, Jin L, Wei Q, Lin D, He F. Association of the variable number of tandem repeats polymorphism in the promoter region of the SMYD3 gene with risk of esophageal squamous cell carcinoma in relation to tobacco smoking. *Cancer Sci* 2008; **99**: 787-791 [PMID: 18294291 DOI: 10.1111/j.1349-7006.2008.00729.x]

71 **Paladino D**, Yue P, Furuya H, Acoba J, Rosser CJ, Turkson J. A novel nuclear Src and p300 signaling axis controls migratory and invasive behavior in pancreatic cancer. *Oncotarget* 2016; **7**: 7253-7267 [PMID: 26695438 DOI: 10.18632/oncotarget.6635]

72 **Kim KH**, Roberts CW. Targeting EZH2 in cancer. *Nat Med* 2016; **22**: 128-134 [PMID: 26845405 DOI: 10.1038/nm.4036]

73 **Bao Y**, Oguz G, Lee WC, Lee PL, Ghosh K, Li J, Wang P, Lobie PE, Ehmsen S, Ditzel HJ, Wong A, Tan EY, Lee SC, Yu Q. EZH2-mediated PP2A inactivation confers resistance to HER2-targeted breast cancer therapy. *Nat Commun* 2020; **11**: 5878 [PMID: 33208750 DOI: 10.1038/s41467-020-19704-x]

74 **Biswas A**, Mukherjee G, Kondaiah P, Desai KV. Both EZH2 and JMJD6 regulate cell cycle genes in breast cancer. *BMC Cancer* 2020; **20**: 1159 [PMID: 33246425 DOI: 10.1186/s12885-020-07531-8]

75 **Chen J**, Wang F, Xu H, Xu L, Chen D, Wang J, Huang S, Wen Y, Fang L. Long Non-Coding RNA SNHG1 Regulates the Wnt/β-Catenin and PI3K/AKT/mTOR Signaling Pathways *via* EZH2 to Affect the Proliferation, Apoptosis, and Autophagy of Prostate Cancer Cell. *Front Oncol* 2020; **10**: 552907 [PMID: 33194612 DOI: 10.3389/fonc.2020.552907]

76 **Jin X**, Yang C, Fan P, Xiao J, Zhang W, Zhan S, Liu T, Wang D, Wu H. CDK5/FBW7-dependent ubiquitination and degradation of EZH2 inhibits pancreatic cancer cell migration and invasion. *J Biol Chem* 2017; **292**: 6269-6280 [PMID: 28242758 DOI: 10.1074/jbc.M116.764407]

77 **Zhou X**, Gao W, Hua H, Ji Z. LncRNA-BLACAT1 Facilitates Proliferation, Migration and Aerobic Glycolysis of Pancreatic Cancer Cells by Repressing CDKN1C *via* EZH2-Induced H3K27me3. *Front Oncol* 2020; **10**: 539805 [PMID: 33072570 DOI: 10.3389/fonc.2020.539805]

78 **Ma J**, Zhang J, Weng YC, Wang JC. EZH2-Mediated microRNA-139-5p Regulates Epithelial-Mesenchymal Transition and Lymph Node Metastasis of Pancreatic Cancer. *Mol Cells* 2018; **41**: 868-880 [PMID: 30304920 DOI: 10.14348/molcells.2018.0109]

79 **Ma Z**, Huang H, Wang J, Zhou Y, Pu F, Zhao Q, Peng P, Hui B, Ji H, Wang K. Long non-coding RNA SNHG15 inhibits P15 and KLF2 expression to promote pancreatic cancer proliferation through EZH2-mediated H3K27me3. *Oncotarget* 2017; **8**: 84153-84167 [PMID: 29137412 DOI: 10.18632/oncotarget.20359]

80 **Rotili D**, Mai A. Targeting Histone Demethylases: A New Avenue for the Fight against Cancer. *Genes Cancer* 2011; **2**: 663-679 [PMID: 21941621 DOI: 10.1177/1947601911417976]

81 **Suzuki T**, Terashima M, Tange S, Ishimura A. Roles of histone methyl-modifying enzymes in development and progression of cancer. *Cancer Sci* 2013; **104**: 795-800 [PMID: 23560485 DOI: 10.1111/cas.12169]

82 **Burg JM**, Link JE, Morgan BS, Heller FJ, Hargrove AE, McCafferty DG. KDM1 class flavin-dependent protein lysine demethylases. *Biopolymers* 2015; **104**: 213-246 [PMID: 25787087 DOI: 10.1002/bip.22643]

83 **Scoumanne A**, Chen X. The lysine-specific demethylase 1 is required for cell proliferation in both p53-dependent and -independent manners. *J Biol Chem* 2007; **282**: 15471-15475 [PMID: 17409384 DOI: 10.1074/jbc.M701023200]

84 **Shi Y**, Whetstine JR. Dynamic regulation of histone lysine methylation by demethylases. *Mol Cell* 2007; **25**: 1-14 [PMID: 17218267 DOI: 10.1016/j.molcel.2006.12.010]

85 **Liu Y**, Zhang JB, Qin Y, Wang W, Wei L, Teng Y, Guo L, Zhang B, Lin Z, Liu J, Ren ZG, Ye QH, Xie Y. PROX1 promotes hepatocellular carcinoma metastasis by way of up-regulating hypoxia-inducible factor 1α expression and protein stability. *Hepatology* 2013; **58**: 692-705 [PMID: 23505027 DOI: 10.1002/hep.26398]

86 **Ouyang H**, Qin Y, Liu Y, Xie Y, Liu J. Prox1 directly interacts with LSD1 and recruits the LSD1/NuRD complex to epigenetically co-repress CYP7A1 transcription. *PLoS One* 2013; **8**: e62192 [PMID: 23626788 DOI: 10.1371/journal.pone.0062192]

87 **Qin Y**, Zhu W, Xu W, Zhang B, Shi S, Ji S, Liu J, Long J, Liu C, Liu L, Xu J, Yu X. LSD1 sustains pancreatic cancer growth *via* maintaining HIF1α-dependent glycolytic process. *Cancer Lett* 2014; **347**: 225-232 [PMID: 24561118 DOI: 10.1016/j.canlet.2014.02.013]

88 **Chen F**, Yang H, Dong Z, Fang J, Wang P, Zhu T, Gong W, Fang R, Shi YG, Li Z, Xu Y. Structural insight into substrate recognition by histone demethylase LSD2/KDM1b. *Cell Res* 2013; **23**: 306-309 [PMID: 23357850 DOI: 10.1038/cr.2013.17]

89 **Ciccone DN**, Su H, Hevi S, Gay F, Lei H, Bajko J, Xu G, Li E, Chen T. KDM1B is a histone H3K4 demethylase required to establish maternal genomic imprints. *Nature* 2009; **461**: 415-418 [PMID: 19727073 DOI: 10.1038/nature08315]

90 **van Essen D**, Zhu Y, Saccani S. A feed-forward circuit controlling inducible NF-κB target gene activation by promoter histone demethylation. *Mol Cell* 2010; **39**: 750-760 [PMID: 20832726 DOI: 10.1016/j.molcel.2010.08.010]

91 **Lin SL**, Chang DC, Lin CH, Ying SY, Leu D, Wu DT. Regulation of somatic cell reprogramming through inducible mir-302 expression. *Nucleic Acids Res* 2011; **39**: 1054-1065 [PMID: 20870751 DOI: 10.1093/nar/gkq850]

92 **Katz TA**, Huang Y, Davidson NE, Jankowitz RC. Epigenetic reprogramming in breast cancer: from new targets to new therapies. *Ann Med* 2014; **46**: 397-408 [PMID: 25058177 DOI: 10.3109/07853890.2014.923740]

93 **Wang Y**, Sun L, Luo Y, He S. Knockdown of KDM1B inhibits cell proliferation and induces apoptosis of pancreatic cancer cells. *Pathol Res Pract* 2019; **215**: 1054-1060 [PMID: 30846414 DOI: 10.1016/j.prp.2019.02.014]

94 **Noble P**, Vyas M, Al-Attar A, Durrant S, Scholefield J, Durrant L. High levels of cleaved caspase-3 in colorectal tumour stroma predict good survival. *Br J Cancer* 2013; **108**: 2097-2105 [PMID: 23591201 DOI: 10.1038/bjc.2013.166]

95 **Cloos PA**, Christensen J, Agger K, Maiolica A, Rappsilber J, Antal T, Hansen KH, Helin K. The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. *Nature* 2006; **442**: 307-311 [PMID: 16732293 DOI: 10.1038/nature04837]

96 **Fodor BD**, Kubicek S, Yonezawa M, O'Sullivan RJ, Sengupta R, Perez-Burgos L, Opravil S, Mechtler K, Schotta G, Jenuwein T. Jmjd2b antagonizes H3K9 trimethylation at pericentric heterochromatin in mammalian cells. *Genes Dev* 2006; **20**: 1557-1562 [PMID: 16738407 DOI: 10.1101/gad.388206]

97 **Klose RJ**, Yamane K, Bae Y, Zhang D, Erdjument-Bromage H, Tempst P, Wong J, Zhang Y. The transcriptional repressor JHDM3A demethylates trimethyl histone H3 Lysine 9 and lysine 36. *Nature* 2006; **442**: 312-316 [PMID: 16732292 DOI: 10.1038/nature04853]

98 **Whetstine JR**, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z, Spooner E, Li E, Zhang G, Colaiacovo M, Shi Y. Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. *Cell* 2006; **125**: 467-481 [PMID: 16603238 DOI: 10.1016/j.cell.2006.03.028]

99 **Agger K**, Cloos PA, Christensen J, Pasini D, Rose S, Rappsilber J, Issaeva I, Canaani E, Salcini AE, Helin K. UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. *Nature* 2007; **449**: 731-734 [PMID: 17713478 DOI: 10.1038/nature06145]

100 **Christensen J**, Agger K, Cloos PA, Pasini D, Rose S, Sennels L, Rappsilber J, Hansen KH, Salcini AE, Helin K. RBP2 belongs to a family of demethylases, specific for tri-and dimethylated lysine 4 on histone 3. *Cell* 2007; **128**: 1063-1076 [PMID: 17320161 DOI: 10.1016/j.cell.2007.02.003]

101 **De Santa F**, Totaro MG, Prosperini E, Notarbartolo S, Testa G, Natoli G. The histone H3 Lysine-27 demethylase Jmjd3 Links inflammation to inhibition of polycomb-mediated gene silencing. *Cell* 2007; **130**: 1083-1094 [PMID: 17825402 DOI: 10.1016/j.cell.2007.08.019]

102 **Frescas D**, Guardavaccaro D, Bassermann F, Koyama-Nasu R, Pagano M. JHDM1B/FBXL10 is a nucleolar protein that represses transcription of ribosomal RNA genes. *Nature* 2007; **450**: 309-313 [PMID: 17994099 DOI: 10.1038/nature06255]

103 **Klose RJ**, Yan Q, Tothova Z, Yamane K, Erdjument-Bromage H, Tempst P, Gilliland DG, Zhang Y, Kaelin WG Jr. The retinoblastoma binding protein RBP2 is an H3K4 demethylase. *Cell* 2007; **128**: 889-900 [PMID: 17320163 DOI: 10.1016/j.cell.2007.02.013]

104 **Lan F**, Bayliss PE, Rinn JL, Whetstine JR, Wang JK, Chen S, Iwase S, Alpatov R, Issaeva I, Canaani E, Roberts TM, Chang HY, Shi Y. A histone H3 Lysine 27 demethylase regulates animal posterior development. *Nature* 2007; **449**: 689-694 [PMID: 17851529 DOI: 10.1038/nature06192]

105 **Tahiliani M**, Mei P, Fang R, Leonor T, Rutenberg M, Shimizu F, Li J, Rao A, Shi Y. The histone H3K4 demethylase SMCX links REST target genes to X-linked mental retardation. *Nature* 2007; **447**: 601-605 [PMID: 17468742 DOI: 10.1038/nature05823]

106 **Yamane K**, Tateishi K, Klose RJ, Fang J, Fabrizio LA, Erdjument-Bromage H, Taylor-Papadimitriou J, Tempst P, Zhang Y. PLU-1 is an H3K4 demethylase involved in transcriptional repression and breast cancer cell proliferation. *Mol Cell* 2007; **25**: 801-812 [PMID: 17363312 DOI: 10.1016/j.molcel.2007.03.001]

107 **Liu W**, Tanasa B, Tyurina OV, Zhou TY, Gassmann R, Liu WT, Ohgi KA, Benner C, Garcia-Bassets I, Aggarwal AK, Desai A, Dorrestein PC, Glass CK, Rosenfeld MG. PHF8 mediates histone H4 Lysine 20 demethylation events involved in cell cycle progression. *Nature* 2010; **466**: 508-512 [PMID: 20622854 DOI: 10.1038/nature09272]

108 **Kim TD**, Oh S, Shin S, Janknecht R. Regulation of tumor suppressor p53 and HCT116 cell physiology by histone demethylase JMJD2D/KDM4D. *PLoS One* 2012; **7**: e34618 [PMID: 22514644 DOI: 10.1371/journal.pone.0034618]

109 **Tzatsos A**, Pfau R, Kampranis SC, Tsichlis PN. Ndy1/KDM2B immortalizes mouse embryonic fibroblasts by repressing the Ink4a/Arf locus. *Proc Natl Acad Sci U S A* 2009; **106**: 2641-2646 [PMID: 19202064 DOI: 10.1073/pnas.0813139106]

110 **Tzatsos A**, Paskaleva P, Lymperi S, Contino G, Stoykova S, Chen Z, Wong KK, Bardeesy N. Lysine-specific demethylase 2B (KDM2B)-let-7-enhancer of zester homolog 2 (EZH2) pathway regulates cell cycle progression and senescence in primary cells. *J Biol Chem* 2011; **286**: 33061-33069 [PMID: 21757686 DOI: 10.1074/jbc.M111.257667]

111 **He J**, Kallin EM, Tsukada Y, Zhang Y. The H3K36 demethylase Jhdm1b/Kdm2b regulates cell proliferation and senescence through p15(Ink4b). *Nat Struct Mol Biol* 2008; **15**: 1169-1175 [PMID: 18836456 DOI: 10.1038/nsmb.1499]

112 **Pfau R**, Tzatsos A, Kampranis SC, Serebrennikova OB, Bear SE, Tsichlis PN. Members of a family of JmjC domain-containing oncoproteins immortalize embryonic fibroblasts *via* a JmjC domain-dependent process. *Proc Natl Acad Sci U S A* 2008; **105**: 1907-1912 [PMID: 18250326 DOI: 10.1073/pnas.0711865105]

113 **Kottakis F**, Polytarchou C, Foltopoulou P, Sanidas I, Kampranis SC, Tsichlis PN. FGF-2 regulates cell proliferation, migration, and angiogenesis through an NDY1/KDM2B-miR-101-EZH2 pathway. *Mol Cell* 2011; **43**: 285-298 [PMID: 21777817 DOI: 10.1016/j.molcel.2011.06.020]

114 **Tzatsos A**, Paskaleva P, Ferrari F, Deshpande V, Stoykova S, Contino G, Wong KK, Lan F, Trojer P, Park PJ, Bardeesy N. KDM2B promotes pancreatic cancer *via* Polycomb-dependent and -independent transcriptional programs. *J Clin Invest* 2013; **123**: 727-739 [PMID: 23321669 DOI: 10.1172/JCI64535]

115 **Yamane K**, Toumazou C, Tsukada Y, Erdjument-Bromage H, Tempst P, Wong J, Zhang Y. JHDM2A, a JmjC-containing H3K9 demethylase, facilitates transcription activation by androgen receptor. *Cell* 2006; **125**: 483-495 [PMID: 16603237 DOI: 10.1016/j.cell.2006.03.027]

116 **Okada Y**, Scott G, Ray MK, Mishina Y, Zhang Y. Histone demethylase JHDM2A is critical for Tnp1 and Prm1 transcription and spermatogenesis. *Nature* 2007; **450**: 119-123 [PMID: 17943087 DOI: 10.1038/nature06236]

117 **Bailey JM**, Alsina J, Rasheed ZA, McAllister FM, Fu YY, Plentz R, Zhang H, Pasricha PJ, Bardeesy N, Matsui W, Maitra A, Leach SD. DCLK1 marks a morphologically distinct subpopulation of cells with stem cell properties in preinvasive pancreatic cancer. *Gastroenterology* 2014; **146**: 245-256 [PMID: 24096005 DOI: 10.1053/j.gastro.2013.09.050]

118 **Dandawate P**, Ghosh C, Palaniyandi K, Paul S, Rawal S, Pradhan R, Sayed AAA, Choudhury S, Standing D, Subramaniam D, Padhye SB, Gunewardena S, Thomas SM, Neil MO, Tawfik O, Welch DR, Jensen RA, Maliski S, Weir S, Iwakuma T, Anant S, Dhar A. The Histone Demethylase KDM3A, Increased in Human Pancreatic Tumors, Regulates Expression of DCLK1 and Promotes Tumorigenesis in Mice. *Gastroenterology* 2019; **157**: 1646-1659.e11 [PMID: 31442435 DOI: 10.1053/j.gastro.2019.08.018]

119 **Labbé RM**, Holowatyj A, Yang ZQ. Histone lysine demethylase (KDM) subfamily 4: structures, functions and therapeutic potential. *Am J Transl Res* 2013; **6**: 1-15 [PMID: 24349617]

120 **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]

121 **Gokturk B**, Artac H, van Eggermond MJ, van den Elsen P, Reisli İ. Type III bare lymphocyte syndrome associated with a novel RFXAP mutation: a case report. *Int J Immunogenet* 2012; **39**: 362-364 [PMID: 22390233 DOI: 10.1111/j.1744-313X.2012.01105.x]

122 **Hanna S**, Etzioni A. MHC class I and II deficiencies. *J Allergy Clin Immunol* 2014; **134**: 269-275 [PMID: 25001848 DOI: 10.1016/j.jaci.2014.06.001]

123 **Li S**, Wu L, Wang Q, Li Y, Wang X. KDM4B promotes epithelial-mesenchymal transition through up-regulation of ZEB1 in pancreatic cancer. *Acta Biochim Biophys Sin (Shanghai)* 2015; **47**: 997-1004 [PMID: 26511091 DOI: 10.1093/abbs/gmv107]

124 **Isohookana J**, Haapasaari KM, Soini Y, Karihtala P. KDM4D Predicts Recurrence in Exocrine Pancreatic Cells of Resection Margins from Patients with Pancreatic Adenocarcinoma. *Anticancer Res* 2018; **38**: 2295-2302 [PMID: 29599352 DOI: 10.21873/anticanres.12474]

125 **Rasmussen PB**, Staller P. The KDM5 family of histone demethylases as targets in oncology drug discovery. *Epigenomics* 2014; **6**: 277-286 [PMID: 25111482 DOI: 10.2217/epi.14.14]

126 **Cui J**, Quan M, Xie D, Gao Y, Guha S, Fallon MB, Chen J, Xie K. A novel KDM5A/MPC-1 signaling pathway promotes pancreatic cancer progression *via* redirecting mitochondrial pyruvate metabolism. *Oncogene* 2020; **39**: 1140-1151 [PMID: 31641207 DOI: 10.1038/s41388-019-1051-8]

127 **Hong S**, Cho YW, Yu LR, Yu H, Veenstra TD, Ge K. Identification of JmjC domain-containing UTX and JMJD3 as histone H3 Lysine 27 demethylases. *Proc Natl Acad Sci U S A* 2007; **104**: 18439-18444 [PMID: 18003914 DOI: 10.1073/pnas.0707292104]

128 **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]

129 **Biankin AV**, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ A, Bruxner T, Cloonan N, Kolle G, Newell F, Pinese M, Mead RS, Humphris JL, Kaplan W, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chou A, Chin VT, Chantrill LA, Mawson A, Samra JS, Kench JG, Lovell JA, Daly RJ, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N; Australian Pancreatic Cancer Genome Initiative, Kakkar N, Zhao F, Wu YQ, Wang M, Muzny DM, Fisher WE, Brunicardi FC, Hodges SE, Reid JG, Drummond J, Chang K, Han Y, Lewis LR, Dinh H, Buhay CJ, Beck T, Timms L, Sam M, Begley K, Brown A, Pai D, Panchal A, Buchner N, De Borja R, Denroche RE, Yung CK, Serra S, Onetto N, Mukhopadhyay D, Tsao MS, Shaw PA, Petersen GM, Gallinger S, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schulick RD, Wolfgang CL, Morgan RA, Lawlor RT, Capelli P, Corbo V, Scardoni M, Tortora G, Tempero MA, Mann KM, Jenkins NA, Perez-Mancera PA, Adams DJ, Largaespada DA, Wessels LF, Rust AG, Stein LD, Tuveson DA, Copeland NG, Musgrove EA, Scarpa A, Eshleman JR, Hudson TJ, Sutherland RL, Wheeler DA, Pearson JV, McPherson JD, Gibbs RA, Grimmond SM. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; **491**: 399-405 [PMID: 23103869 DOI: 10.1038/nature11547]

130 **Hoadley KA**, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, Leiserson MDM, Niu B, McLellan MD, Uzunangelov V, Zhang J, Kandoth C, Akbani R, Shen H, Omberg L, Chu A, Margolin AA, Van't Veer LJ, Lopez-Bigas N, Laird PW, Raphael BJ, Ding L, Robertson AG, Byers LA, Mills GB, Weinstein JN, Van Waes C, Chen Z, Collisson EA; Cancer Genome Atlas Research Network, Benz CC, Perou CM, Stuart JM. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. *Cell* 2014; **158**: 929-944 [PMID: 25109877 DOI: 10.1016/j.cell.2014.06.049]

131 **van Haaften G**, Dalgliesh GL, Davies H, Chen L, Bignell G, Greenman C, Edkins S, Hardy C, O'Meara S, Teague J, Butler A, Hinton J, Latimer C, Andrews J, Barthorpe S, Beare D, Buck G, Campbell PJ, Cole J, Forbes S, Jia M, Jones D, Kok CY, Leroy C, Lin ML, McBride DJ, Maddison M, Maquire S, McLay K, Menzies A, Mironenko T, Mulderrig L, Mudie L, Pleasance E, Shepherd R, Smith R, Stebbings L, Stephens P, Tang G, Tarpey PS, Turner R, Turrell K, Varian J, West S, Widaa S, Wray P, Collins VP, Ichimura K, Law S, Wong J, Yuen ST, Leung SY, Tonon G, DePinho RA, Tai YT, Anderson KC, Kahnoski RJ, Massie A, Khoo SK, Teh BT, Stratton MR, Futreal PA. Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. *Nat Genet* 2009; **41**: 521-523 [PMID: 19330029 DOI: 10.1038/ng.349]

132 **Waddell N**, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, Quinn MC, Robertson AJ, Fadlullah MZ, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Wilson PJ, Markham E, Cloonan N, Anderson MJ, Fink JL, Holmes O, Kazakoff SH, Leonard C, Newell F, Poudel B, Song S, Taylor D, Waddell N, Wood S, Xu Q, Wu J, Pinese M, Cowley MJ, Lee HC, Jones MD, Nagrial AM, Humphris J, Chantrill LA, Chin V, Steinmann AM, Mawson A, Humphrey ES, Colvin EK, Chou A, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Pettitt JA, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, Graham JS, Niclou SP, Bjerkvig R, Grützmann R, Aust D, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Falconi M, Zamboni G, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Gill AJ, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Pearson JV, Biankin AV, Grimmond SM. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518**: 495-501 [PMID: 25719666 DOI: 10.1038/nature14169]

133 **Witkiewicz AK**, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, Mollaee M, Wagner KU, Koduru P, Yopp A, Choti MA, Yeo CJ, McCue P, White MA, Knudsen ES. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun* 2015; **6**: 6744 [PMID: 25855536 DOI: 10.1038/ncomms7744]

134 **Welstead GG**, Creyghton MP, Bilodeau S, Cheng AW, Markoulaki S, Young RA, Jaenisch R. X-linked H3K27me3 demethylase Utx is required for embryonic development in a sex-specific manner. *Proc Natl Acad Sci U S A* 2012; **109**: 13004-13009 [PMID: 22826230 DOI: 10.1073/pnas.1210787109]

135 **Agger K**, Cloos PA, Rudkjaer L, Williams K, Andersen G, Christensen J, Helin K. The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev* 2009; **23**: 1171-1176 [PMID: 19451217 DOI: 10.1101/gad.510809]

136 **Barradas M**, Anderton E, Acosta JC, Li S, Banito A, Rodriguez-Niedenführ M, Maertens G, Banck M, Zhou MM, Walsh MJ, Peters G, Gil J. Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev* 2009; **23**: 1177-1182 [PMID: 19451218 DOI: 10.1101/gad.511109]

137 **Kanda M**, Matthaei H, Wu J, Hong SM, Yu J, Borges M, Hruban RH, Maitra A, Kinzler K, Vogelstein B, Goggins M. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology* 2012; **142**: 730-733.e9 [PMID: 22226782 DOI: 10.1053/j.gastro.2011.12.042]

138 **Yamamoto K**, Tateishi K, Kudo Y, Sato T, Yamamoto S, Miyabayashi K, Matsusaka K, Asaoka Y, Ijichi H, Hirata Y, Otsuka M, Nakai Y, Isayama H, Ikenoue T, Kurokawa M, Fukayama M, Kokudo N, Omata M, Koike K. Loss of histone demethylase KDM6B enhances aggressiveness of pancreatic cancer through downregulation of C/EBPα. *Carcinogenesis* 2014; **35**: 2404-2414 [PMID: 24947179 DOI: 10.1093/carcin/bgu136]

139 **Pan MR**, Hsu MC, Chen LT, Hung WC. G9a orchestrates PCL3 and KDM7A to promote histone H3K27 methylation. *Sci Rep* 2015; **5**: 18709 [PMID: 26688070 DOI: 10.1038/srep18709]

140 **Aasland R**, Gibson TJ, Stewart AF. The PHD finger: implications for chromatin-mediated transcriptional regulation. *Trends Biochem Sci* 1995; **20**: 56-59 [PMID: 7701562 DOI: 10.1016/s0968-0004(00)88957-4]

141 **Sanchez R**, Zhou MM. The PHD finger: a versatile epigenome reader. *Trends Biochem Sci* 2011; **36**: 364-372 [PMID: 21514168 DOI: 10.1016/j.tibs.2011.03.005]

142 **Ali M**, Hom RA, Blakeslee W, Ikenouye L, Kutateladze TG. Diverse functions of PHD fingers of the MLL/KMT2 subfamily. *Biochim Biophys Acta* 2014; **1843**: 366-371 [PMID: 24291127 DOI: 10.1016/j.bbamcr.2013.11.016]

143 **Yokoyama A**, Ficara F, Murphy MJ, Meisel C, Naresh A, Kitabayashi I, Cleary ML. Proteolytically cleaved MLL subunits are susceptible to distinct degradation pathways. *J Cell Sci* 2011; **124**: 2208-2219 [PMID: 21670200 DOI: 10.1242/jcs.080523]

144 **Wang J**, Muntean AG, Wu L, Hess JL. A subset of mixed lineage leukemia proteins has plant homeodomain (PHD)-mediated E3 Ligase activity. *J Biol Chem* 2012; **287**: 43410-43416 [PMID: 23129768 DOI: 10.1074/jbc.M112.423855]

145 **Chang PY**, Hom RA, Musselman CA, Zhu L, Kuo A, Gozani O, Kutateladze TG, Cleary ML. Binding of the MLL PHD3 finger to histone H3K4me3 is required for MLL-dependent gene transcription. *J Mol Biol* 2010; **400**: 137-144 [PMID: 20452361 DOI: 10.1016/j.jmb.2010.05.005]

146 **Mathioudaki A**, Ljungström V, Melin M, Arendt ML, Nordin J, Karlsson Å, Murén E, Saksena P, Meadows JRS, Marinescu VD, Sjöblom T, Lindblad-Toh K. Targeted sequencing reveals the somatic mutation landscape in a Swedish breast cancer cohort. *Sci Rep* 2020; **10**: 19304 [PMID: 33168853 DOI: 10.1038/s41598-020-74580-1]

147 **Dhar SS**, Lee SH, Kan PY, Voigt P, Ma L, Shi X, Reinberg D, Lee MG. Trans-tail regulation of MLL4-catalyzed H3K4 methylation by H4R3 symmetric dimethylation is mediated by a tandem PHD of MLL4. *Genes Dev* 2012; **26**: 2749-2762 [PMID: 23249737 DOI: 10.1101/gad.203356.112]

148 **Ali M**, Rincón-Arano H, Zhao W, Rothbart SB, Tong Q, Parkhurst SM, Strahl BD, Deng LW, Groudine M, Kutateladze TG. Molecular basis for chromatin binding and regulation of MLL5. *Proc Natl Acad Sci U S A* 2013; **110**: 11296-11301 [PMID: 23798402 DOI: 10.1073/pnas.1310156110]

149 **Lemak A**, Yee A, Wu H, Yap D, Zeng H, Dombrovski L, Houliston S, Aparicio S, Arrowsmith CH. Solution NMR structure and histone binding of the PHD domain of human MLL5. *PLoS One* 2013; **8**: e77020 [PMID: 24130829 DOI: 10.1371/journal.pone.0077020]

150 **Klose RJ**, Kallin EM, Zhang Y. JmjC-domain-containing proteins and histone demethylation. *Nat Rev Genet* 2006; **7**: 715-727 [PMID: 16983801 DOI: 10.1038/nrg1945]

151 **Torres IO**, Kuchenbecker KM, Nnadi CI, Fletterick RJ, Kelly MJ, Fujimori DG. Histone demethylase KDM5A is regulated by its reader domain through a positive-feedback mechanism. *Nat Commun* 2015; **6**: 6204 [PMID: 25686748 DOI: 10.1038/ncomms7204]

152 **Tsai WW**, Wang Z, Yiu TT, Akdemir KC, Xia W, Winter S, Tsai CY, Shi X, Schwarzer D, Plunkett W, Aronow B, Gozani O, Fischle W, Hung MC, Patel DJ, Barton MC. TRIM24 Links a non-canonical histone signature to breast cancer. *Nature* 2010; **468**: 927-932 [PMID: 21164480 DOI: 10.1038/nature09542]

153 **Hillringhaus L**, Yue WW, Rose NR, Ng SS, Gileadi C, Loenarz C, Bello SH, Bray JE, Schofield CJ, Oppermann U. Structural and evolutionary basis for the dual substrate selectivity of human KDM4 histone demethylase family. *J Biol Chem* 2011; **286**: 41616-41625 [PMID: 21914792 DOI: 10.1074/jbc.M111.283689]

154 **Trojer P**, Zhang J, Yonezawa M, Schmidt A, Zheng H, Jenuwein T, Reinberg D. Dynamic Histone H1 Isotype 4 Methylation and Demethylation by Histone Lysine Methyltransferase G9a/KMT1C and the Jumonji Domain-containing JMJD2/KDM4 Proteins. *J Biol Chem* 2009; **284**: 8395-8405 [PMID: 19144645 DOI: 10.1074/jbc.M807818200]

155 **Berry WL**, Janknecht R. KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells. *Cancer Res* 2013; **73**: 2936-2942 [PMID: 23644528 DOI: 10.1158/0008-5472.CAN-12-4300]

156 **Højfeldt JW**, Agger K, Helin K. Histone lysine demethylases as targets for anticancer therapy. *Nat Rev Drug Discov* 2013; **12**: 917-930 [PMID: 24232376 DOI: 10.1038/nrd4154]

157 **Iwase S**, Lan F, Bayliss P, de la Torre-Ubieta L, Huarte M, Qi HH, Whetstine JR, Bonni A, Roberts TM, Shi Y. The X-linked mental retardation gene SMCX/JARID1C defines a family of histone H3 Lysine 4 demethylases. *Cell* 2007; **128**: 1077-1088 [PMID: 17320160 DOI: 10.1016/j.cell.2007.02.017]

158 **Wang GG**, Song J, Wang Z, Dormann HL, Casadio F, Li H, Luo JL, Patel DJ, Allis CD. Haematopoietic malignancies caused by dysregulation of a chromatin-binding PHD finger. *Nature* 2009; **459**: 847-851 [PMID: 19430464 DOI: 10.1038/nature08036]

159 **Zhang Y**, Yang H, Guo X, Rong N, Song Y, Xu Y, Lan W, Zhang X, Liu M, Xu Y, Cao C. The PHD1 finger of KDM5B recognizes unmodified H3K4 during the demethylation of histone H3K4me2/3 by KDM5B. *Protein Cell* 2014; **5**: 837-850 [PMID: 24952722 DOI: 10.1007/s13238-014-0078-4]

160 **Shi X**, Hong T, Walter KL, Ewalt M, Michishita E, Hung T, Carney D, Peña P, Lan F, Kaadige MR, Lacoste N, Cayrou C, Davrazou F, Saha A, Cairns BR, Ayer DE, Kutateladze TG, Shi Y, Côté J, Chua KF, Gozani O. ING2 PHD domain links histone H3 Lysine 4 methylation to active gene repression. *Nature* 2006; **442**: 96-99 [PMID: 16728974 DOI: 10.1038/nature04835]

161 **Johansson C**, Velupillai S, Tumber A, Szykowska A, Hookway ES, Nowak RP, Strain-Damerell C, Gileadi C, Philpott M, Burgess-Brown N, Wu N, Kopec J, Nuzzi A, Steuber H, Egner U, Badock V, Munro S, LaThangue NB, Westaway S, Brown J, Athanasou N, Prinjha R, Brennan PE, Oppermann U. Structural analysis of human KDM5B guides histone demethylase inhibitor development. *Nat Chem Biol* 2016; **12**: 539-545 [PMID: 27214403 DOI: 10.1038/nchembio.2087]

162 **Peng Y**, Alexov E. Cofactors-loaded quaternary structure of lysine-specific demethylase 5C (KDM5C) protein: Computational model. *Proteins* 2016; **84**: 1797-1809 [PMID: 27696497 DOI: 10.1002/prot.25162]

163 **Zhu Z**, Wang Y, Li X, Wang Y, Xu L, Wang X, Sun T, Dong X, Chen L, Mao H, Yu Y, Li J, Chen PA, Chen CD. PHF8 is a histone H3K9me2 demethylase regulating rRNA synthesis. *Cell Res* 2010; **20**: 794-801 [PMID: 20531378 DOI: 10.1038/cr.2010.75]

164 **Horton JR**, Upadhyay AK, Qi HH, Zhang X, Shi Y, Cheng X. Enzymatic and structural insights for substrate specificity of a family of jumonji histone lysine demethylases. *Nat Struct Mol Biol* 2010; **17**: 38-43 [PMID: 20023638 DOI: 10.1038/nsmb.1753]

165 **Zhang H**, Song Y, Yang C, Wu X. UHRF1 mediates cell migration and invasion of gastric cancer. *Biosci Rep* 2018; **38** [PMID: 30352833 DOI: 10.1042/bsr20181065]

166 **Guo X**, Xu Y, Wang P, Li Z, Xu Y, Yang H. Crystallization and preliminary crystallographic analysis of a PHD domain of human JARID1B. *Acta Crystallogr Sect F Struct Biol Cryst Commun* 2011; **67**: 907-910 [PMID: 21821892 DOI: 10.1107/S1744309111021981]

167 **Thompson B**, Townsley F, Rosin-Arbesfeld R, Musisi H, Bienz M. A new nuclear component of the Wnt signalling pathway. *Nat Cell Biol* 2002; **4**: 367-373 [PMID: 11988739 DOI: 10.1038/ncb786]

168 **Wang J**, Zhong M, Liu B, Sha L, Lun Y, Zhang W, Li X, Wang X, Cao J, Ning A, Huang M. Expression and functional analysis of novel molecule - Latcripin-13 domain from Lentinula edodes C91-3 produced in prokaryotic expression system. *Gene* 2015; **555**: 469-475 [PMID: 25447899 DOI: 10.1016/j.gene.2014.11.014]

169 **Qian Y**, Gong Y, Fan Z, Luo G, Huang Q, Deng S, Cheng H, Jin K, Ni Q, Yu X, Liu C. Molecular alterations and targeted therapy in pancreatic ductal adenocarcinoma. *J Hematol Oncol* 2020; **13**: 130 [PMID: 33008426 DOI: 10.1186/s13045-020-00958-3]

170 **Manuyakorn A**, Paulus R, Farrell J, Dawson NA, Tze S, Cheung-Lau G, Hines OJ, Reber H, Seligson DB, Horvath S, Kurdistani SK, Guha C, Dawson DW. Cellular histone modification patterns predict prognosis and treatment response in resectable pancreatic adenocarcinoma: results from RTOG 9704. *J Clin Oncol* 2010; **28**: 1358-1365 [PMID: 20142597 DOI: 10.1200/JCO.2009.24.5639]

171 **Hinton J**, Callan R, Bodine C, Glasgow W, Brower S, Jiang SW, Li J. Potential epigenetic biomarkers for the diagnosis and prognosis of pancreatic ductal adenocarcinomas. *Expert Rev Mol Diagn* 2013; **13**: 431-443 [PMID: 23782251 DOI: 10.1586/erm.13.38]

172 **Mazur PK**, Reynoird N, Khatri P, Jansen PW, Wilkinson AW, Liu S, Barbash O, Van Aller GS, Huddleston M, Dhanak D, Tummino PJ, Kruger RG, Garcia BA, Butte AJ, Vermeulen M, Sage J, Gozani O. SMYD3 Links lysine methylation of MAP3K2 to Ras-driven cancer. *Nature* 2014; **510**: 283-287 [PMID: 24847881 DOI: 10.1038/nature13320]

173 **Peserico A**, Germani A, Sanese P, Barbosa AJ, Di Virgilio V, Fittipaldi R, Fabini E, Bertucci C, Varchi G, Moyer MP, Caretti G, Del Rio A, Simone C. A SMYD3 Small-Molecule Inhibitor Impairing Cancer Cell Growth. *J Cell Physiol* 2015; **230**: 2447-2460 [PMID: 25728514 DOI: 10.1002/jcp.24975]

174 **Driehuis E**, van Hoeck A, Moore K, Kolders S, Francies HE, Gulersonmez MC, Stigter ECA, Burgering B, Geurts V, Gracanin A, Bounova G, Morsink FH, Vries R, Boj S, van Es J, Offerhaus GJA, Kranenburg O, Garnett MJ, Wessels L, Cuppen E, Brosens LAA, Clevers H. Pancreatic cancer organoids recapitulate disease and allow personalized drug screening. *Proc Natl Acad Sci U S A* 2019 [PMID: 31818951 DOI: 10.1073/pnas.1911273116]

175 **Avan A**, Crea F, Paolicchi E, Funel N, Galvani E, Marquez VE, Honeywell RJ, Danesi R, Peters GJ, Giovannetti E. Molecular mechanisms involved in the synergistic interaction of the EZH2 inhibitor 3-deazaneplanocin A with gemcitabine in pancreatic cancer cells. *Mol Cancer Ther* 2012; **11**: 1735-1746 [PMID: 22622284 DOI: 10.1158/1535-7163.MCT-12-0037]

176 **Andricovich J**, Perkail S, Kai Y, Casasanta N, Peng W, Tzatsos A. Loss of KDM6A Activates Super-Enhancers to Induce Gender-Specific Squamous-like Pancreatic Cancer and Confers Sensitivity to BET Inhibitors. *Cancer Cell* 2018; **33**: 512-526.e8 [PMID: 29533787 DOI: 10.1016/j.ccell.2018.02.003]

177 **Yamamoto K**, Tateishi K, Kudo Y, Hoshikawa M, Tanaka M, Nakatsuka T, Fujiwara H, Miyabayashi K, Takahashi R, Tanaka Y, Ijichi H, Nakai Y, Isayama H, Morishita Y, Aoki T, Sakamoto Y, Hasegawa K, Kokudo N, Fukayama M, Koike K. Stromal remodeling by the BET bromodomain inhibitor JQ1 suppresses the progression of human pancreatic cancer. *Oncotarget* 2016; **7**: 61469-61484 [PMID: 27528027 DOI: 10.18632/oncotarget.11129]

178 **King ON**, Li XS, Sakurai M, Kawamura A, Rose NR, Ng SS, Quinn AM, Rai G, Mott BT, Beswick P, Klose RJ, Oppermann U, Jadhav A, Heightman TD, Maloney DJ, Schofield CJ, Simeonov A. Quantitative high-throughput screening identifies 8-hydroxyquinolines as cell-active histone demethylase inhibitors. *PLoS One* 2010; **5**: e15535 [PMID: 21124847 DOI: 10.1371/journal.pone.0015535]

179 **Jin C**, Yang L, Xie M, Lin C, Merkurjev D, Yang JC, Tanasa B, Oh S, Zhang J, Ohgi KA, Zhou H, Li W, Evans CP, Ding S, Rosenfeld MG. Chem-seq permits identification of genomic targets of drugs against androgen receptor regulation selected by functional phenotypic screens. *Proc Natl Acad Sci U S A* 2014; **111**: 9235-9240 [PMID: 24928520 DOI: 10.1073/pnas.1404303111]

180 **Sonnemann J**, Zimmermann M, Marx C, Ebert F, Becker S, Lauterjung ML, Beck JF. LSD1 (KDM1A)-independent effects of the LSD1 inhibitor SP2509 in cancer cells. *Br J Haematol* 2018; **183**: 494-497 [PMID: 29205263 DOI: 10.1111/bjh.14983]

181 **Fang Y**, Liao G, Yu B. LSD1/KDM1A inhibitors in clinical trials: advances and prospects. *J Hematol Oncol* 2019; **12**: 129 [PMID: 31801559 DOI: 10.1186/s13045-019-0811-9]

182 **Yamagishi M**, Uchimaru K. Targeting EZH2 in cancer therapy. *Curr Opin Oncol* 2017; **29**: 375-381 [PMID: 28665819 DOI: 10.1097/CCO.0000000000000390]

183 **Kuang Y**, Lu F, Guo J, Xu H, Wang Q, Xu C, Zeng L, Yi S. Histone demethylase KDM2B upregulates histone methyltransferase EZH2 expression and contributes to the progression of ovarian cancer *in vitro* and in vivo. *Onco Targets Ther* 2017; **10**: 3131-3144 [PMID: 28706445 DOI: 10.2147/OTT.S134784]

184 **Lawrence MS**, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, Meyerson M, Gabriel SB, Lander ES, Getz G. Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature* 2014; **505**: 495-501 [PMID: 24390350 DOI: 10.1038/nature12912]

185 **Ler LD**, Ghosh S, Chai X, Thike AA, Heng HL, Siew EY, Dey S, Koh LK, Lim JQ, Lim WK, Myint SS, Loh JL, Ong P, Sam XX, Huang D, Lim T, Tan PH, Nagarajan S, Cheng CW, Ho H, Ng LG, Yuen J, Lin PH, Chuang CK, Chang YH, Weng WH, Rozen SG, Tan P, Creasy CL, Pang ST, McCabe MT, Poon SL, Teh BT. Loss of tumor suppressor KDM6A amplifies PRC2-regulated transcriptional repression in bladder cancer and can be targeted through inhibition of EZH2. *Sci Transl Med* 2017; **9** [PMID: 28228601 DOI: 10.1126/scitranslmed.aai8312]

186 **Au SL**, Wong CC, Lee JM, Fan DN, Tsang FH, Ng IO, Wong CM. Enhancer of zeste homolog 2 epigenetically silences multiple tumor suppressor microRNAs to promote liver cancer metastasis. *Hepatology* 2012; **56**: 622-631 [PMID: 22370893 DOI: 10.1002/hep.25679]

187 **Mitra D**, Das PM, Huynh FC, Jones FE. Jumonji/ARID1 B (JARID1B) protein promotes breast tumor cell cycle progression through epigenetic repression of microRNA let-7e. *J Biol Chem* 2011; **286**: 40531-40535 [PMID: 21969366 DOI: 10.1074/jbc.M111.304865]

188 **Kwak YT**, Guo J, Prajapati S, Park KJ, Surabhi RM, Miller B, Gehrig P, Gaynor RB. Methylation of SPT5 regulates its interaction with RNA polymerase II and transcriptional elongation properties. *Mol Cell* 2003; **11**: 1055-1066 [PMID: 12718890 DOI: 10.1016/s1097-2765(03)00101-1]

189 **Jansson M**, Durant ST, Cho EC, Sheahan S, Edelmann M, Kessler B, La Thangue NB. Arginine methylation regulates the p53 response. *Nat Cell Biol* 2008; **10**: 1431-1439 [PMID: 19011621 DOI: 10.1038/ncb1802]

190 **Han T**, Jiao F, Hu H, Yuan C, Wang L, Jin ZL, Song WF, Wang LW. EZH2 promotes cell migration and invasion but not alters cell proliferation by suppressing E-cadherin, partly through association with MALAT-1 in pancreatic cancer. *Oncotarget* 2016; **7**: 11194-11207 [PMID: 26848980 DOI: 10.18632/oncotarget.7156]

191 **Kooistra SM**, Helin K. Molecular mechanisms and potential functions of histone demethylases. *Nat Rev Mol Cell Biol* 2012; **13**: 297-311 [PMID: 22473470 DOI: 10.1038/nrm3327]

192 **Pfister SX**, Ahrabi S, Zalmas LP, Sarkar S, Aymard F, Bachrati CZ, Helleday T, Legube G, La Thangue NB, Porter AC, Humphrey TC. SETD2-dependent histone H3K36 trimethylation is required for homologous recombination repair and genome stability. *Cell Rep* 2014; **7**: 2006-2018 [PMID: 24931610 DOI: 10.1016/j.celrep.2014.05.026]

193 **Lee GS**, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky R, Sacks DB, Germain RN, Kastner DL, Chae JJ. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca2+ and cAMP. *Nature* 2012; **492**: 123-127 [PMID: 23143333 DOI: 10.1038/nature11588]

194 **Khoury-Haddad H**, Nadar-Ponniah PT, Awwad S, Ayoub N. The emerging role of lysine demethylases in DNA damage response: dissecting the recruitment mode of KDM4D/JMJD2D to DNA damage sites. *Cell Cycle* 2015; **14**: 950-958 [PMID: 25714495 DOI: 10.1080/15384101.2015.1014147]

195 **Horton JR**, Liu X, Gale M, Wu L, Shanks JR, Zhang X, Webber PJ, Bell JSK, Kales SC, Mott BT, Rai G, Jansen DJ, Henderson MJ, Urban DJ, Hall MD, Simeonov A, Maloney DJ, Johns MA, Fu H, Jadhav A, Vertino PM, Yan Q, Cheng X. Structural Basis for KDM5A Histone Lysine Demethylase Inhibition by Diverse Compounds. *Cell Chem Biol* 2016; **23**: 769-781 [PMID: 27427228 DOI: 10.1016/j.chembiol.2016.06.006]

196 **Gong F**, Clouaire T, Aguirrebengoa M, Legube G, Miller KM. Histone demethylase KDM5A regulates the ZMYND8-NuRD chromatin remodeler to promote DNA repair. *J Cell Biol* 2017; **216**: 1959-1974 [PMID: 28572115 DOI: 10.1083/jcb.201611135]

197 **Liu H**, Liu L, Holowatyj A, Jiang Y, Yang ZQ. Integrated genomic and functional analyses of histone demethylases identify oncogenic KDM2A isoform in breast cancer. *Mol Carcinog* 2016; **55**: 977-990 [PMID: 26207617 DOI: 10.1002/mc.22341]

198 **Longbotham JE**, Chio CM, Dharmarajan V, Trnka MJ, Torres IO, Goswami D, Ruiz K, Burlingame AL, Griffin PR, Fujimori DG. Histone H3 binding to the PHD1 domain of histone demethylase KDM5A enables active site remodeling. *Nat Commun* 2019; **10**: 94 [PMID: 30626866 DOI: 10.1038/s41467-018-07829-z]

199 **Lan F**, Collins RE, De Cegli R, Alpatov R, Horton JR, Shi X, Gozani O, Cheng X, Shi Y. Recognition of unmethylated histone H3 Lysine 4 Links BHC80 to LSD1-mediated gene repression. *Nature* 2007; **448**: 718-722 [PMID: 17687328 DOI: 10.1038/nature06034]

200 **Fair K**, Anderson M, Bulanova E, Mi H, Tropschug M, Diaz MO. Protein interactions of the MLL PHD fingers modulate MLL target gene regulation in human cells. *Mol Cell Biol* 2001; **21**: 3589-3597 [PMID: 11313484 DOI: 10.1128/mcb.21.10.3589-3597.2001]

201 **Li SS**, Jiang WL, Xiao WQ, Li K, Zhang YF, Guo XY, Dai YQ, Zhao QY, Jiang MJ, Lu ZJ, Wan R. KMT2D deficiency enhances the anti-cancer activity of L48H37 in pancreatic ductal adenocarcinoma. *World J Gastrointest Oncol* 2019; **11**: 599-621 [PMID: 31435462 DOI: 10.4251/wjgo.v11.i8.599]

202 **Zhang X**, Novera W, Zhang Y, Deng LW. MLL5 (KMT2E): structure, function, and clinical relevance. *Cell Mol Life Sci* 2017; **74**: 2333-2344 [PMID: 28188343 DOI: 10.1007/s00018-017-2470-8]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interests or financial disclosures relevant to this manuscript.

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**Manuscript source:** Invited manuscript

**Peer-review started:** January 27, 2021

**First decision:** February 25, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Kobayashi S, Tada M **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:**

**Table 1 Histone methyltransferases play a major role in** **pancreatic cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Family** | **Subfamily** | **Alias** | **Site** | **Function in pancreatic cancer** |
|
| PRMTs | PRMT1 | HRMT1L2, HMT2, ANM1 | H4R3me2a | Increase the β-catenin protein level; Methylate Gli1 at R597[44,54] |
| PRMT5 | HRMT1L5, SKB1, HSL7 | H3R2me2s | Silence the expression of the tumor suppressor FBW7; Promote EMT *via* activating EGFR/ AKT/β-catenin signaling[45,56,188,189] |
| KMTs | SMYD3 | ZNFN3A1, ZMYND1 | H4K5me3 | Affect the PC progression by regulating MMP-2; Potentiate Ras signaling through methylation of MAP3K2[62,64] |
| EZH2 | KMT6, WVS, ENX-1 | H3K27me3 | Suppress miR-139-5p expression by upregulating H3K27me3; Repress the E-cadherin by tri-methylation of H3K27[78,190] |

All current research on reprogramming histone methyltransferases that play a role in pancreatic cancer. EMT: Epithelial-mesenchymal transition; FBW7: F-Box and WD repeat domain containing 7; KMTs: Histone lysine methyltransferases; PC: Pancreatic cancer; PRMTs: Protein arginine N-methyltransferases.

**Table 2 Histone demethylase that plays a major role in pancreatic cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Family** | **Subfamily** | **Alias** | **Site** | **Function in pancreatic cancer** |
|
| KDM1 | KDM1A | LSD1 | H3K4me1 | Promote the occurrence of cancer[83] |
| KDM1B | LSD2, AOF1 | H3K4me2 | Related to tumor tissue apoptosis[84] |
| Jumonji C | KDM2B | Ndy1, FBXL10, JHDM1B | H3K4me3, H3K36me2 | Promote senescence of primary cells[109,110] |
| KDM3A | JMJD1A, JHDM2A | H3K9me2 (preferential), H3K9me1 | Regulate biological and pathological processes, including embryonic development, stem cell self-renewal and differentiation, genome integrity and tumorigenesis[191,192] |
| KDM4 family | KDM4A | JMJD2A | H3K36me3, H3K9me3 | Destruction of homologous recombination[120,138] |
| KDM4B | JMJD2B | H3K9me3 | Promote epithelial-mesenchymal transition[123] |
| KDM4D | JMJD2D | H3K9me2/me3 | Stimulates *in vitro* proliferation and cell survival, and plays a vital role in DNA double-strand break repair[193,194] |
| KDM5A | JARID1A, RBBP2 | H3K4me2 | Promote the inhibition of active transcription and repair of DNA double-strand breaks[139,195] |
| KDM6 family | KDM6A | UTX | H3K27me2/me3 | The effect of KDM6A on PC tissue is currently unclear[196] |
| KDM6B | JMJD3 | H3K27me2/me3 | Enhance the aggressiveness of cancer cells[176] |
| PHD finger and zinc finger protein family | KDM7A | JHDM1D | H3K9me2, H3K27me2 | May be related to the upregulation of E-cadherin gene expression[93] |

All current research on reprogramming histone demethylases that play a role in pancreatic cancer. The table is sorted by family. PC: Pancreatic cancer; PHD: Plant homeodomain.

**Table 3 Different enzymes and plant homeodomain finger domain**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of enzyme** | **Name of enzyme** | **PHD domain** | **Histone Substrates** | **Function** |
| Histone demethylation enzyme | KDM1B/LSD2 | PHD | H3K4me2 | Unknown[25] |
| KDM2A | PHD | H3K36me2/me1 | Unknown[150] |
| KDM4A-C | Two PHD | Unknown | Unknown[155,197] |
| KDM5A | PHD1 | Unmethylated H3K4 histone tail | PHD1 finger by H3 N-terminal tail peptides stabilizes binding of the substrate to the catalytic finger and improves the catalytic efficiency of demethylation[198,199] |
| PHD2 | Unmodified H3K4 | Unknown[158] |
| PHD3 | H3K4me3 | PHD3 finger can recruit substrate and it relates to demethylation propagation along nucleosomes *via* a positive-feedback regulatory mechanism[151,199] |
| KDM5B | PHD1 | H3K4me0 | PHD1 finger recognizes the N-terminus of histone H3, provides an anchoring mechanism for KDM5B and PHD1-H3K4me0 is interaction is important for inhibition of migration[17] |
| PHD2 | Couldn’t bind to histone | Unknown[17] |
| PHD3 | H3K4me3/H3K4me0 | PHD3 finger detects H3K4me3, anchors at chromatin and spreads the transcriptionally inactive state |
| KDM5C | PHD1 | H3K4 | PHD1 finger stabilizes the substrate peptide and helps to position the H3K4 in the JmjC finger exactly[162] |
| PHF8(KDM7subfamily) | PHD1 | Suppressive marks on H3K9me2/me3 and H3K27me2/me3 and H4k20me2/me3 | PHD1 finger plays a significant role in PHF8 substrate recognition and helps to improve substrate affinity and specificity[164] |
| Histone methylation enzyme | KMT2A, KMT2B | PHD1 | Unknown | PHD1 finger is necessary for a context-dependent regulation of holocomplex formation and implicated in tumor suppression[143] |
| PHD2 | Unknown | PHD2 finger shows the E3 ubiquitin ligase activity and involve in homo-dimerization[144,200]. Mutation in PHD2 will enhance transactivation ability and help to recruit target gene promoters |
| PHD3 | H3K4me3/me2 | Unclear, one possibility is binding of H3K4me3 by PHD3 is necessary for the transcription-promoting effects of KMT2A/2B, another is to set a broad, methylated chromatin finger[145] |
| PHD4 | Unknown | PHD4 finger mediates intramolecular interactions between the N-terminal and C-terminal fragments of KMT2A with PHD1, and improves its stability[143] |
| KMT2C | Eight PHD fingers | Unknown | These fingers help KMT2C to recruit to its target genes correctly[30,146] |
| KMT2D | Seven PHD fingers | Unmodified histone H4 and asymmetrical H4R3me2 | These fingers are [essential](http://www.baidu.com/link?url=1Dn-LSS-7p28fov0j595sO28x-n6SPW3FYKteHp1ElMzn44Z9goUtDsNIu-2dqyn3XuIewkEDRTdSSm5qCm4jFOI8AtfsvpdKhkvVU78VYi) for methyltransferase activity of KMT2D and KMT2D-mediated differentiation[201] |
| KMT2E | PHD | H3K4me3 | PHD finger binds to H3K4me3 specially and facilitates the recruitment of KMT2E to active transcription chromatin regions[148,149,202] |

All current research on the regulation of writers and erasers by plant homeodomain domain. “Unknown” means that the corresponding literature was not mentioned. This table is sorted by types and subfamilies of enzymes. JmjC: Jumonji C; KMT: Histone lysine methyltransferase; PHD: Plant homeodomain.

**Table 4 Inhibitors for the treatment of pancreatic cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug type** | **Drug name** | **Active site**  | **Mechanism** | **Effect** | **Targeting tumors** |
| Relating to histone methyltransferase | SMYD3 inhibitor piperidine-4-formamide-acetylaniline compound (BCI-121) | It competes with histones to bind SMYD3, binding sites are formed within the SET and post-SET fingers and contained in a deep and narrow substrate binding cavity | BCI-121 is a competitive inhibitor significantly inhibits; SMYD3-substrate interaction and chromatin recruitment | It inhibits cancer cell growth and accumulates during the cell cycle S | High expression of SMYD3 protein in cancer cell lines (pancreatic cancer, lung, prostate and ovarian cancer)[173] |
| PRMT5 inhibitor EZP015556 | MTAP | - | It works for MTAP He and MTAP PDO | A negative tumor MTAP (a commonly lost gene in pancreatic cancer)[174] |
| EZH2 inhibitor 3-Dazocycline A (DZNeP) | It regulates EZH2 and H3K27me3 protein expression | DZNeP inhibit the activity of S-adenosine-L-homocysteine (AdoHcy) hydrolase, which reversely hydrolyzes AdoHcy to adenosine and homocysteine, thereby inhibiting histone methylation | It synergistically enhanced antiproliferative activity of gemcitabine and significantly increased apoptosis rate | Pancreatic ductal carcinoma[175] |
| Relating to histone demethylase | BET inhibitor JQ1 related to KDM6A | Reducing activity and p63 levels of MYC pathways | GLI1 is the main target gene of the Hh pathway JQ1 reduces the mRNA and protein levels of primary human CAFs. TGF-β is an interstitial activator that JQ1 its induced response | Altered KMT2C (MLL3)-KDM6A (UTX)- PRC2 regulating axis | Pancreatic ductal carcinoma[169,176,177] |

All current research on inhibitors for the treatment of pancreatic cancer developed based on histone methylation modification. “-” means that the content does not exist here. This table is sorted according to the correlation with histone methyltransferases and demethylases. CAF: Cancer-associated fibroblast; KMT: Histone lysine methyltransferases; PDO: Patient-derived organoid; PRC2: Polycomb repressive complex 2; TGF-β: Transforming growth factor β.