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Exploring the Role of Histone Lysine Methyl Transferases in Pancreatic Cancer: A Review of Therapeutics and Clinical Implications

Abilash Navaneethan[1], Mrithika Ajay[1], Karnika Yogeswari Makesh[1], Ganesh Munuswamy-Ramanujam[2], Rameshbabu Boga[3], Dhanavathy Gnanasampanthapandian[1*] and Kanagaraj Palaniyandi[1*]

[1]Cancer Science Laboratory, Department of Biotechnology, SRM Institute of Science and Technology, Kattankulathur – 603203, Tamil Nadu, India; muthammal.kanagaraj@gmail.com, dhanavathy.2006@gmail.com

[2]Interdisciplinary Institute of Indian System of Medicine, SRM Institute of Science and Technology, Kattankulathur – 603203, Tamil Nadu, India

[3]BogaR Laboratories Private Limited, Hyderabad – 500072, Telangana, India

Abstract

Histone Lysine Methyl Transferases (HKMTs) are pivotal epigenetic regulators that modulate chromatin structure and gene expression, thereby influencing various cellular processes, and their molecular mechanisms and functional significance in health and disease are being elucidated. We discuss the involvement of HKMTs in a number of diseases, including cancer, neurodegenerative disorders, and metabolic diseases, and emphasise the importance of their conserved regions and interactions with histone substrates. In addition, we explore the therapeutic potential of HKMT inhibitors in the treatment of these diseases, highlighting their promising efficacy and potential advantages over conventional therapies. Despite the encouraging clinical outcomes, it remains difficult to understand the specificity and long-term consequences of HKMT inhibition, so further research and clinical evaluation are required. This review provides valuable insights into the complex regulatory role of HKMTs in epigenetic processes and offers perspectives for the development of novel therapeutic strategies with clinical implications for pancreatic cancer.

Keywords: Cancer, Epigenetics, Histone Methyl Transferase, Inhibitors, Pancreases

1. Introduction

Chromatin regulation is an essential component of the epigenetic regulatory mechanism[1]. Epigenetic regulation indirectly plays an important role in transcription, DNA repair, and replication processes[2]. Methylation is one of these important mechanisms of chromatin regulation, in which both histone and non-histone proteins are modified by the addition of methyl groups[3]. The methyl groups are attached from S-adenosylmethionine (SAM) as mono-, di-, or tri-methyl residues, adding one, two, or three methyl units, respectively[4]. Although methylation is hardly associated with significant changes in polypeptide arrangement, it is closely related to the functionality of promoters and enhancers, depending on the extent to which methylation is performed[5]. Methylation occurs either in the histone or non-histone subunit of lysine residues. Usually, promoters are trimethylated as H3K4me3, and the enhancers are mono- or di-methylated as H3K4me1 or H3K4me2, respectively[6-9].

Among the various post-translational modifications, such as acetylation, ubiquitination, methylation, and sumoylation, methylation is the most important process that alters chromatin regulation and its availability for transcription[10]. Histone methylation causes a shift in chromatin condensation and allows for an "open" state associated with increased transcription or a "closed" state associated with decreased transcription in a particular chromatin segment[11]. Proteins containing the SET domain, such as Su(var)3-9, enhancer-of-zeste, and

**Author for correspondence*
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Trithorax, as well as Dot1-like proteins, are involved in the methylation of lysine[12]. Residues and the protein arginine N-methyltransferase (PRMT) family, which methylates arginine residues, can facilitate histone methylation[13] (Figure 1). Histone modifications have vital functions in gene regulation and chromatin remodelling, and their dysregulation can lead to carcinogenesis and various developmental disorders[14]. Histone Methyltransferases (HMTs) are intriguing therapeutic targets due to their diversity and high specificity. Although the number of HMT inhibitors is currently limited, only a few have made it into clinical trials[15-17]. Analysis of cancer genomes revealed a significant frequency of mutations in chromatin-related genes, some of which are oncogenic transformation factors[8,9]. Cancer cells exhibit a disrupted epigenome due to abnormal growth, metabolic reprogramming, and mutations in metabolic enzymes[6,18,19]. As a result, chemicals that affect the epigenetic landscape have been developed rationally: Epidrugs have shown remarkable anti-cancer activities in preclinical models, and their therapeutic use is currently under investigation[20,21]. The first generation of epidrugs, consisting of histone deacetylase inhibitors and DNA demethylating agents, showed limited efficacy and toxicity; therefore, a second generation of more selective and mechanism-targeted compounds is currently being developed[22-25].

In the area of endocrine function, epigenetics serves as a link between genetics and the environment. This means that hormone levels can change in response to internal and external environmental changes. Normal metabolism is regulated by the digestive system, the neuronal system, and the endocrine system[26]. The study of epigenetic regulation in type 1 and type II diabetes mellitus is a very important area in regenerative medicine[27]. Therefore, the timing of epigenetic effects on the endocrine system throughout the lifespan is crucial[28]. β-cell dysfunction and failure related to epigenetic regulation play an important role in type II diabetes mellitus[29]. Epigenetic editing plays a vital role in the rejuvenation of β-cells[30].

Pancreatic cancer is a highly aggressive type of cancer with a high mortality rate and a low survival rate[31]. Aberrant expression of epigenetic regulators leads to the development and progression of PC[32].

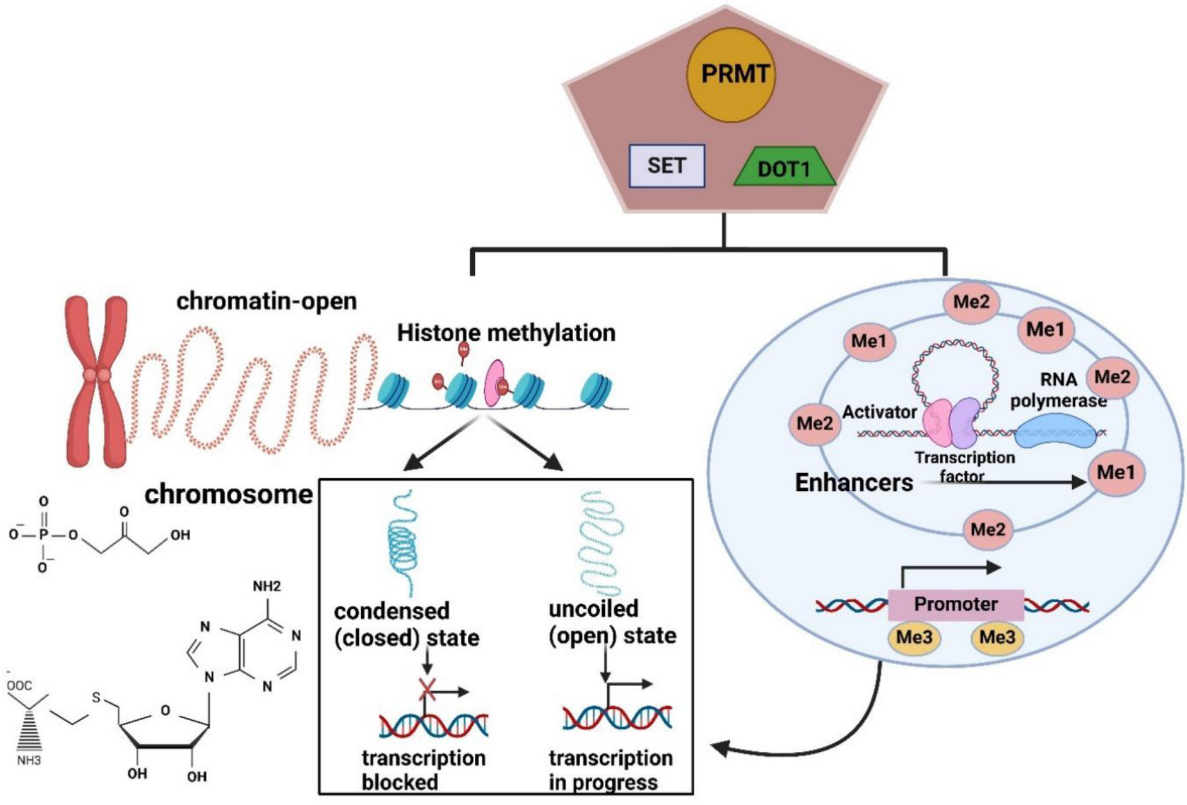


Figure 1. PRMTs, SET, and DOT1 mediate the attachment of methyl groups from S-adenosylmethionine to the histone subunits and thus regulate transcription through the condensation and opening of chromatin structures.

2. Characteristics of Pancreatic Cancer

An effective understanding of the molecular basis of PC is vital for the development of biomarkers or for a comprehensive idea of how to develop a treatment strategy. The initiation and progression of PC associated with the accumulation of variations in multiple genes is thought to be central to the process of carcinogenesis, which in turn leads to deregulation of oncogenic Signaling pathways[33]. Histologically, tumours consist not only of homogeneous cells but also of much more than just the extracellular and cellular tissue scaffold, the stroma, which interacts with the cancer cells[34]. Histopathologic studies have identified three major precursor lesions in PC, namely Mucinous Cystic Neoplasms (MCN), Pancreatic Intraepithelial Neoplasia (PanIN), and Intraductal Papillary Mucinous Neoplasia (IPMN), with PanIN being the most commonly observed[34]. Pancreatic cancer has a broad spectrum and is classified as epithelial or non-epithelial based on its histologic differentiation[35]. Depending on its behaviour, it is classified as benign, premalignant, or malignant, while epithelial cancer can be either endocrine or exocrine[35]. The exocrine type of cancer is also divided into two types, such as ductal and acinar neoplasms[36]. Pancreatic Ductal Adenocarcinoma (PDAC) is the most common type of pancreatic cancer and accounts for ~90% of all PC cases[37]. Under the microscope, PDAC consists of atypical tubular glands that resemble medium-sized or smaller pancreatic ducts, with diverse and heterogeneous growth patterns both within and between tumours, although non-tubular structures, such as clear cell, cribriform, and gyriform patterns, may also affect patient survival[38]. Highly sensitive techniques to detect the Kristen Rat Sarcoma viral oncogene (*KRAS*) mutations show that more than 99% of stage 1 PanIN-1 lesions harbour this mutation[39]. Nearly 90% of pancreatic tumours of all grades have activated *KRAS* mutations[40]. In low-grade early-stage PanIN-1 lesions, mutations in the *KRAS* oncogene homolog occur together with overexpression of oncogenic miRNAs and activation of stromal-associated factors[33]. The prominent genetic alterations associated with the progression of PanIN are well established. PanIN grades 1 and 2 are distinguished by point mutations in *KRAS* and telomerase shortening[41]. Grade 2 is associated with increased activation of CDKN2A and CDKN1A55, while grades 3 and 4 are related to *TP53* mutations (50–70%) and *SMAD4* mutations (60–90%)[41]. Nuclear accumulation of TP53 or loss of *SMAD4* is indicated in PanIN-3 and invasive cancer, and the frequency of somatic alteration of both genes is higher in invasive cancer[33]. The main function is to inhibit cell proliferation by inducing cell cycle arrest in the G1 phase. This tumour suppressor protein was found either deleted or mutated in pancreatic cancer[33]. The main function is to inhibit cell proliferation by inducing a cell cycle arrest in G1 phase, and this tumour suppressor protein has been reported to be either deleted or mutated in pancreatic cancer[42]. Intermediate lesions (PanIN-2) are associated with overexpression of mucin 1 (MUC1) and inactivation of mutations in p16/CDKN2A, whereas late lesions (PanIN-3) are associated with inactivation of mutations in tumour suppressor protein p53, breast cancer type 2 susceptibility protein (BRCA2), and maternal against decapentaplegic homolog 4 (SMAD4)[33]. More somatic mutations are observed in PDAC samples identified by next-generation sequencing, with most mutations occurring in common pathways: RAS signaling pathways, transforming Growth Factor beta (TGFβ) signaling pathways, cell-cycle control, WNT signaling pathways, NOTCH signaling pathways, and DNA damage repair[41]. The major oncogene identified in PC cells is mutant activation of KRAS, with the frequency of KRAS increasing with disease progression[34]. GAT (aspartic acid; G12D), GTT (valine; G12V), and TGT (cysteine; G12C) are the most common oncogenic *KRAS* mutations in human pancreatic cancer, while CGT (arginine (Arg); G12R) and GCT (alanine; G12A) and other point mutations at codons 11, 13, 61, or 146 are less common[40]. Although KRAS plays a central role in the process of carcinogenesis, the KRAS inhibitors are still unknown. Therefore, conventional cytotoxic agents, which produce a significant response in most patients, are currently used as standard therapy but have limited efficacy[43]. c-MYC is a proto-oncogene that plays a central role in the regulation of cell function in normal and cancerous cells. Studies have shown that the oncogene influences protein expression, and thus promotes cell transformation, proliferation, cell cycle progression, stemness of cells, and metabolic processes of the cells[33]. The mutation of c-MYC expression alone does not serve as a driving factor for PC development, but together with the *KRAS* gene mutation, it triggers

tumorigenesis[33]. This situation has led to the need for further research to find additional novel features and susceptibilities of PDAC[43].

3. Histone Lysine Methyl Transferases (HKMT)

The addition of methyl groups is carried out by enzymes called lysine methyltransferases, and the removal of methyl groups is assisted by lysine demethylases, commonly referred to as 'writers' and 'erasers', respectively. Methylation occurs at two histone subunits, H3 and H4. The histone H3 subunit has methylations at lysine residues 4 (H3K4), 9 (H3K9), 27 (H3K27), 36 (H3K36), and 79 (H3K79), as well as at the histone H4 (H4K20) subunit, which is methylated at the lysine residue 20, whose functions are very important in various chromosomal processes, and these HKMTs are more specific in their functions[44]. Methylations at H3K4, H3K36, and H3K79 are associated with active transcription, whereas methylations at H3K9, H3K27, and H4K20 are associated with silenced chromatin states[45,46]. Su(var)3–9, the Enhancer of zeste and Trithorax (SET) domain and the Seven-beta-strand (7βS) domain are the two major domains of HKMTs. There are 55 SET domains, half of which are active methyltransferases, and there are nearly 150–160 7βS domains[8,47]. There are several sites in the human histone subunits where methylation occurs, such as SET 1A/1B/7/9, MLL 1-4, SMYD 1/2, PRDM9 in the H3K4 subunit; SUV39H1/2, G9a, GLP, SETDB1, PRDM family in the H3K9 subunit; EZH1/2 in the H3K27 subunit; SETD2/3, NSD1-3, SMYD2, ASH1L, SETMAR in the H3K36 subunit; and DOT1L in the H3K79 subunit and SET8, SUV4-20H1/2 in the H4K20 subunit[48]. The most abundant histone methyltransferases are the H3K4 methyltransferases (H3K4MT). These H3K4MT also possess several molecular cross-links with each other to perform specific functions, such as those with H3K9 and H3K27, which simultaneously mark bivalent chromatin, leading to the transition of gene expression from a balanced to an active or inactive state in embryonic stem cells[14,49].

4. Clinical Significance of HKMTs

The modification of histone proteins can result in a gene being either expressed or repressed, depending on its position and state. Studies in plants have shown that several mutations in the histone methyltransferases lead to different developmental and growth defects[14]. A study on EZH2 shows that it is involved in the development of chronic renal disease and acute kidney injury (AKI) due to abnormal expression or activity[13,50]. HKMTs are associated with various cancers, such as lung, colorectal, pancreatic, oesophageal, hepatocellular, and cervical cancer[51,52].

5. HKMTs in Cancers

Numerous HKMT sites have been identified as being involved in cancer development and progression. In humans, several missense mutations have been identified that are associated with different types of cancer, *e.g.*, 95% of chondroblastomas with K36M mutations (lysine 36 to methionine)[53], giant cell tumours of bone with G34W/L mutations (glycine 34 to tryptophan or leucine)[54], pediatric gliomas with G34R/V mutations (glycine 34 to arginine/valine) and K27M mutations (lysine 27 to methionine)[55]. It is evident that these onco-histones (cancer-causing histones) have methylations near their post-translational modification sites, such as H3K27 and H3K36[56]. Lewis *et al.*[57] have reported the significance of the H3K27M mutation in improving the condition of glioblastomas by inhibiting repressive polycomb complex 2 (PRC2), *i.e.*, a gain-of-function mutation to treat pathologies.

Mutations in histones have been detected in bone neoplasms. H3K27M and H3G34V/R have been reported in high-grade pediatric gliomas[58]. In addition, various histone mutations play a specific role in the pathogenesis of diseases[59]. Faundes *et al.*[60] used human variation databases and published animal models to investigate that haploinsufficiency of KMT genes plays an important role in developmental disorders in humans. EZH2 is not only a catalytic component of the Polycomb Repressive Complex 2 (PRC2), but also an epigenetic regulator that modulates gene expression by trimethylating the lysine 27 residue on histone 3 (H3K27). EZH2 is known for its significant role in carcinogenesis and could therefore be of great benefit for cancer therapies through therapeutic intervention[61]. EZH2 is involved in the initiation of fibroblast activation, renal fibrosis, and partial epithelial-to-mesenchymal transition (EMT)[62].

There are several mutations in the HKMTs that regulate functional genes either as a whole or in part. Targeting the HKMTs responsible for disease pathogenesis would be of great benefit for improving health status.

Therefore, inhibitors of HKMTs that prevent aberrant histone methylation are in increased need. Among all epigenetic changes, histone methylation is one of the most complex and has been shown to play a critical role in the progression of PC[63].

The pancreas exhibits considerable heterogeneity and comprises different cell types with different functions. As the pancreas acts as a hub for hormonal regulation of glucose homeostasis, meticulous control of gene expression is required to ensure accurate synthesis and secretion of hormones. There are divergent perspectives on the epigenetic changes in the genes encoding pancreatic hormones[64].

The observed absence or limited presence of active promoter modifications in the genes encoding islet-specific hormones indicates the association of different regulatory mechanisms. In addition, enhancer-mediated regulation of islet-specific hormones has been demonstrated by genome-wide analysis of DNase I hypersensitive sites and examination of histone H3 lysine methylation[65]. Studies suggest a reduction in overall histone methylation (specifically H3K4me3) and acetylation (H3K9/14ac) in individuals with insulin resistance (IR)[66]. Bhandare *et al.*[67] also found that H3K4me2 and me3 levels at the promoters of insulin and glucagon genes are significantly reduced in human islets. Their results suggest that the MAF bZIP transcription factor (MAFB), which is responsible for glucagon gene activation, has a promoter in human pancreatic α-cells characterised by an H3K4me3 modification that facilitates activation of both MAFB and the glucagon gene. In β-cells, the PDX1 enhancer showed an enrichment of H3K4me1[68]. Consequently, epigenetic modifications at the promoters of transcription factors play a crucial role in the regulation of islet-specific hormones. Moreover, H3K27me3 was enriched in the promoter of NEUROG3, another islet-specific transcription factor, consistent with its downregulation in adult pancreatic islets[67]. In contrast to β-cells and exocrine cells, studies have shown that α-cells in islets have more bivalent modified histone modifications (H3K4me3 for transcriptional activation and H3K27me3 for transcriptional repression), whereas β-cells have many genes with monovalent histone modifications (either H3K4me3 or H3K27me3). These results suggest that epigenetic modifications play a role in the differentiation and dedifferentiation processes of pancreatic islet α- and β-cells[69]. Histone modifications play a pivotal role in determining the fate of pancreatic progenitor cells, differentiation, and function of α- and β-cells, as shown in Figure 2[26,70].

Alpha cells are the source of glucagon, a hormone that causes blood glucose levels to rise. Although it is often referred to as "diabetogenic," glucagon plays a crucial role in maintaining glucose homeostasis by preventing hypoglycemia, especially during fasting or exercise[71]. Dysregulation of glucagon secretion, and not glucagon itself, contributes to the hyperglycemia observed in diabetes[72]. The ability of α-cells to transform into β-cells is an active area of research and holds therapeutic potential. This plasticity could be harnessed to regenerate β-cell mass in people with diabetes[73]. The local production of GLP-1 within α-cells, which exerts paracrine effects on β-cells and promotes their growth and survival. Glutamate co-released with glucagon enhances glucagon secretion under hypoglycemic conditions via a positive feedback loop[74,75]. This mechanism ensures a rapid response to low glucose levels and contributes to the restoration of normoglycemia. Impaired glucose sensing is a hallmark of α-cell dysfunction in type 2 diabetes. This defect leads to inappropriately increased glucagon secretion, which exacerbates hyperglycemia[75]. The blunted response to hypoglycemia is another critical aspect of α-cell dysfunction in diabetes and increases the risk of severe hypoglycemic episodes. This impaired counter-regulatory response underscores the importance of addressing both insulin and glucagon dysregulation in the treatment of diabetes[76]. Alpha cell function can usually be assessed by an arginine simulation test. The exaggerated glucagon response to arginine observed in people with type 2 diabetes confirms the dysregulation of glucagon secretion in this disease. Although isoproterenol is also used in provocation tests, it is primarily used to assess β-cell function[77]. In addition to glucagon, α-cells also secrete other factors with autocrine and paracrine signaling properties that contribute to the complicated islet microenvironment. A better understanding of these factors and their interactions within the islet is required to fully understand the role of α-cells in health and disease. The pathway of glucose-stimulated insulin secretion is relevant to understanding β-cell function but is less directly related to α-cell physiology[78].

PDX-1 is a transcription factor that is essential for pancreatic development, differentiation of β-cells, and maintenance of mature β-cell function by regulating β-cell-related genes[79]. It is also essential for the differentiation and maintenance of the β-cell phenotype

by transactivating the insulin gene and regulating important glucose-sensing and metabolic genes, such as GLUT2 and glucokinase, in mature β-cells[70,80]. To investigate the role of PDX-1 in pancreas formation and maintenance, genetically engineered mice were generated using the Tet-off system in which PDX-1 expression was regulated by tetracycline or doxycycline. In these mice, the endogenous PDX-1 gene was replaced with a tetracycline-regulated transactivator (tTA) that activated a transgene encoding PDX-1 in the absence of doxycycline, thus rescuing the null phenotype, while doxycycline-mediated suppression during gestation mimicked the PDX-1-null condition[81]. Suppression of PDX-1 arrested development midway through pancreogenesis, decreased insulin biosynthesis in adult mice, and disrupted glucose homeostasis, emphasising its essential role in pancreatic development, β-cell differentiation, and mature β-cell function[82]. In diabetes studies, a type 2 diabetes mouse model using low-dose streptozotocin showed that α-cell mass was preserved while β-cell mass was reduced by 75%[83]. Similarly, pancreas samples from individuals with autoimmune type 1 or type 2 diabetes showed that overall α-cell mass was preserved, although the donor varied. A study of 47 cases of type 1 diabetes showed a slight overall reduction, with some pancreatic cells showing no change or a significant increase compared to non-diabetic, age-matched controls, while in type 2 diabetes, α-cell mass was largely preserved[83]. Regeneration studies found that administration of streptozotocin to 4-day-old rat pups activated Ngn3 and Pax4 in α-cells, contributed to the maintenance of α-cell mass, and restored 60% of β-cell mass by day 20[79].

In their study, Bramswig *et al.*[84] demonstrated that exposure of cultured pancreatic islets to a histone methyltransferase inhibitor leads to the coexistence of glucagon and insulin and to the simultaneous presence of glucagon and insulin promoter factor 1 (PDX1) in human islets (Figure 3).

In the development of pancreatic cancer, histone deacetylases (HDACs) play an important role in

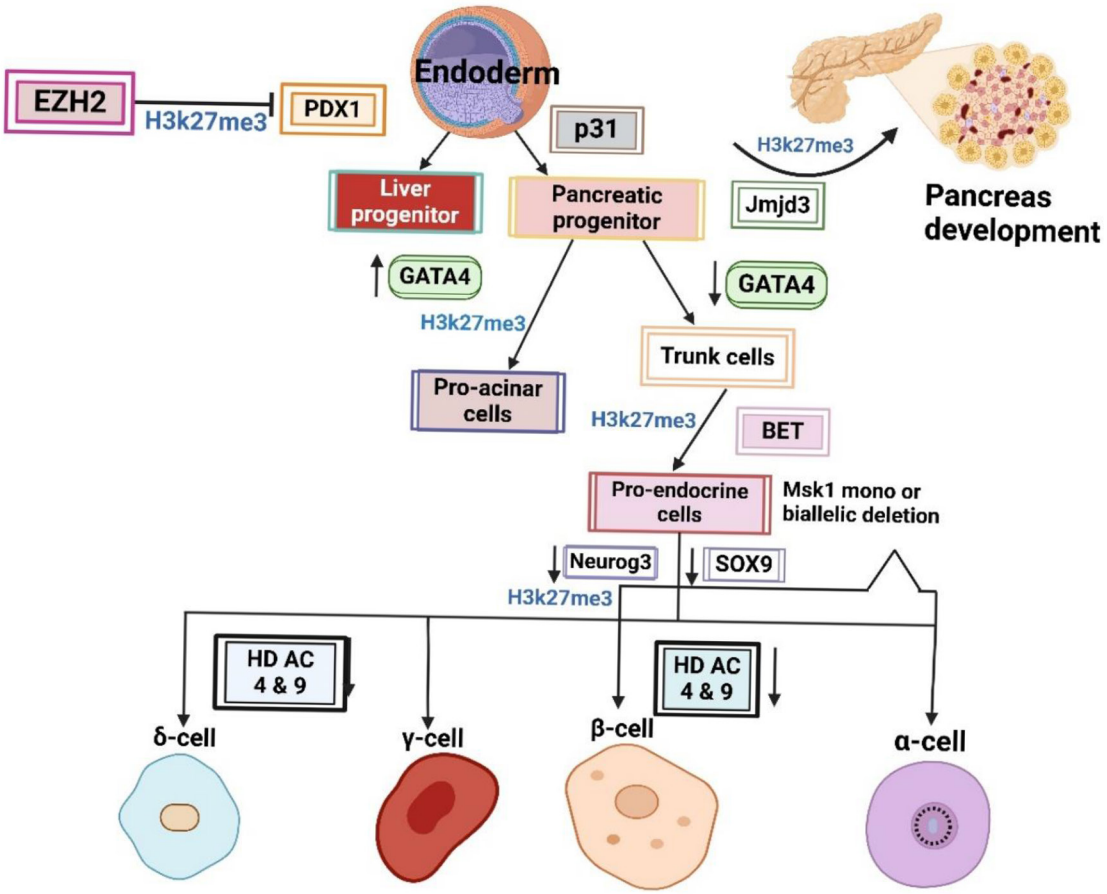


Figure 2. Diagram illustrating the effects of histone modifications on the pancreatic development and the functions of α- and β-cells.

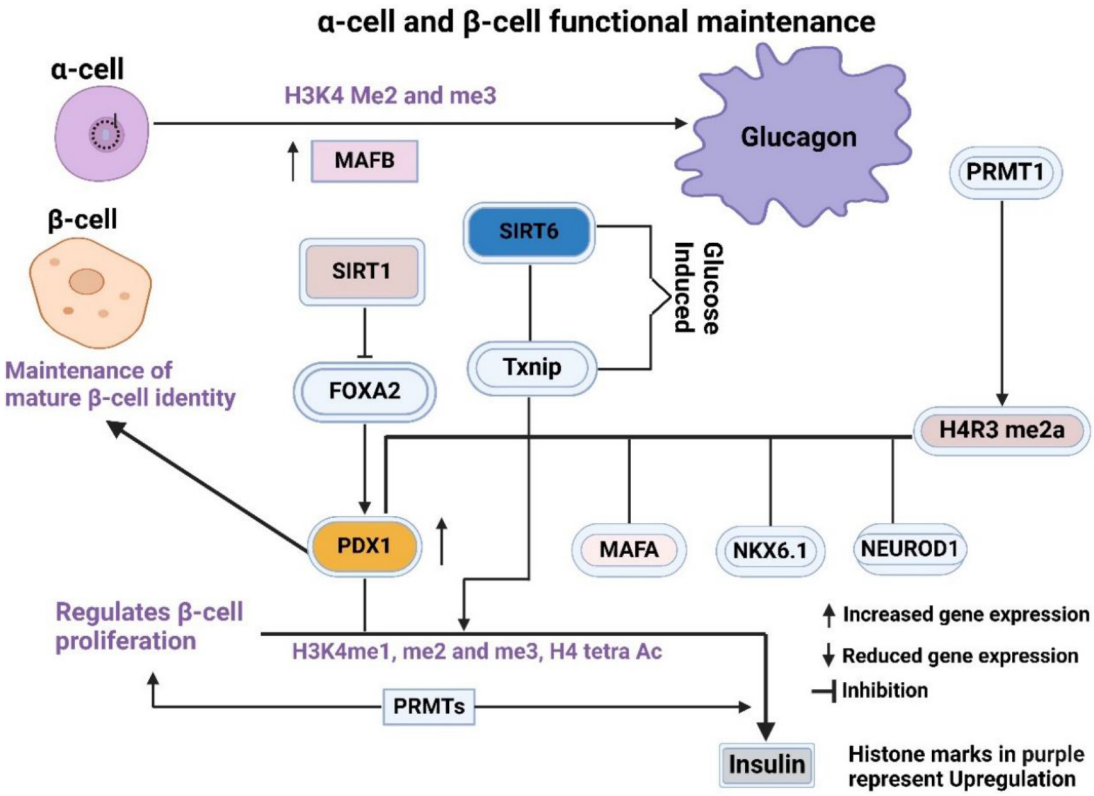


Figure 3. Various histone modifiers and their effects on progenitor cell fate have been indicated by arrows. The focus is on histone modifications that control the functions of endocrine cells, particularly α- and β-cells, which play a central role in regulating insulin metabolism and insulin signaling. Red stands for the removal of histone marks and purple for the addition of histone marks.

regulating the epigenetic aspects of development. Abnormal expression of HDACs has been associated with various human diseases, with a particular focus on their involvement in cancer[85]. In particular, HDAC1 has been extensively studied for its contribution to exocrine pancreatic morphogenesis and PC development[62,86]. Regulation of Somatostatin Receptor (SSTR) expression likely involves DNA methylation and histone acetylation, which affect the transition between heterochromatin and euchromatin[87]. However, there is little information on the epigenetic regulation of SSTR in other cancers. Hypermethylation of the SST promoter has been demonstrated in pancreatic PANC-1 cells[87]. Hartman *et al.*[88] investigated the relationship between HDAC and the activation of trypsin, inflammation, and tissue damage in severe acute pancreatitis. They treated C57Bl/6 mice with taurocholic acid, which induced pancreatitis, and administered the HDAC inhibitor trichostatin A (TSA). A significant decrease in amylase levels and a decrease in systemic IL-6 and pulmonary myeloperoxidase activity were observed. In addition, the pancreas showed a reduction in taurocholate-induced gene expression of cyclooxygenase-2, MIP-2, MCP-1, IL-6, and IL-1β[89].

6. Interconnection among HKMT, Immune Cells, and Hormone-Secreting Pancreatic Cells

HKMTs are a class of enzymes that play a significant role in the epigenetic regulation of gene expression[51]. These enzymes catalyse the transfer of a methyl group from the cofactor S-adenosylmethionine (SAM) to the ε-amino group on the lysine residues of histone tails by performing a reaction known as methylation[51]. Lysines can be mono-, di-, or trimethylated, and a specific form of each modification may be associated with a specific downstream effect on chromatin structure and gene transcription. The formation of S-adenosylhomocysteine occurs after methyl group transfer, *i.e.*, the catalytic cycle is complete[90].

The catalytically active centre of HKMTs is characterised by two distinct pockets: a SAM-binding pocket and a lysine acceptor channel. These pockets are located on different sides of the enzyme surface, allowing both SAM and the target lysine substrate to bind to the enzyme independently[91,92]. The methylene group of the incoming lysine chain is involved in the formation of the channel by establishing stable interactions through the van der Waals contacts with the aromatic residues that form the channel[91]. At the same time, the ε-amino group of lysine forms a hydrogen bond with the hydroxyl group of tyrosine, the catalytic residue in the highly conserved SET domain[93]. The interplay of all these actions is the precise positioning of the lysine substrate for methyl group transfer[91,93].

Extensive research has focused on the study of HKMTs in the functions of cells and their involvement in diseases, especially cancer. Basically, studies have classified the HKMTs-specific targets of inhibitors, such as BRD9539 and its analogue BRD4770[94]. These inhibitors have shown promising results in preclinical studies, through two mechanisms: they downregulate G9a activity, which plays a key role in HKMTs, thereby reducing methylation of H3K9 in PC cells[95]. This change in H3K9 methylation, which is typically associated with gene silencing, would have significant effects on gene expression and cell behaviour[96].

It has been shown that the use of HKMT inhibitors leads to senescence, *i.e.*, an irreparable arrest of the cell cycle, which slows down the proliferation of PC cell lines[97]. This observation suggests that inhibition of HKMTs could be a very attractive therapeutic direction to stop the uncontrolled growth of PC cells. Equally interesting is the fact that inhibition of HKMTs is correlated with higher expression of SPINK1, a massive protease inhibitor, pancreatic secretory trypsin inhibitor[98]. Mutations in the *SPINK1* gene have been associated with chronic pancreatitis, indicating the complexity of the relationship among HKMTs, gene expression, and disease[99].

The inhibitory effect of HKMTs goes beyond the levels of cell growth and gene expression. Studies have shown that inhibition of HKMTs has a major impact on autophagy, a critical cellular process for cell clearance and recycling[100,101]. For instance, the study by Montenegro *et al.*[100] found that treatment of PC cells with an HMT inhibitor effectively blocks the formation of autophagosomes, such that HMT activity is required for the initial stages of autophagy. Furthermore, HMT was found to be responsible for the growth of lysosome diameter in PC cells, a situation that has been associated with lysosomal stress and poor proteolysis[68]. HMT Setd7 plays an important role in promoting pancreatic progenitor cell identity[100,102]. In addition, p62/SQSTM1, the protein marker for blocking autophagy, accumulated under HMT inhibition, convincing the given proposition[100,103]. It was also found that the combination of HMT inhibition with other therapeutic agents such as the BH3 mimetic gossypol, dramatically increased pancreatic cancer[100].

Although treatment of PANC1 cells with DIPY alone did not significantly modify the intracellular levels of SAM and SAH, we observed that the inclusion of TMCG in the treatment resulted in a consistent and significant decrease in the methylation capacity of PANC1 cells[104]. Yuan *et al.*[104] state that the discovery of BRD4770, a mimetic S-adenosylmethionine inhibitor of G9a, promotes senescence in PANC-1 cells lacking functional p53 and p16.

Histone methyltransferases are an important component of gene expression, which can be characterised as such by altering methylation. G9a and EZH2 are particularly important in gene silencing by H3K9 and H3K27 methylation, respectively[105,106]. They regulate gene expression of T-cell exhaustion, which is a state of reduced function in chronic infections and cancer[105,107]. It was found that in HCV-specific CD8+ T cells from patients with chronic infections, H3K9 dimethylation was higher, implying that G9a was responsible for this process[108]. Therefore, it is possible that G9a strongly drives the depletion of T helper cells due to the non-expression of genes involved in their functions[109].

The efficacy and safety of HMT inhibitors specifically targeting G9a and EZH2 have been studied in animal models with promising results[107,110]. T-cell function was restored by treatment with these inhibitors after increasing IFNγ and TNFα production from control cytokines[111]. In addition, inhibition of dimethylation of H3K9 was observed upon treatment with these inhibitors, suggesting that it is a reversal of repressive chromatin that leads to T-cell exhaustion[107]. TP53, the tumour suppressor that formed the basis for these inhibitors, together with HMT, enhanced these effects, demonstrating the possible relationship between these pathways[112].

Beyond mere effect on T-cell exhaustion, HMTs and SUV39H1 and EZH2 play a more as T-cell modulators in T-cell differentiation. SUV39H1 does this by trimethylating H3K9 to generate heterochromatin at Th1

gene promoters, which means that Th1 differentiation is inhibited and Th2 lineage commitment is favoured[113]. Similarly, a lack of differentiation of the T follicle helper cell type occurs when EZH2 is absent[114].

HMT, G9a, and EZH2 their involved in the depletion of T-cell function in chronic disease, and the marked improvements in outcomes of HMT inhibitors confirm that they are potential targets for treatment[115]. To obtain a complete picture, more research is needed on how T cells interact with these HMTs in this way and how these findings can be used in clinical practice to help people suffering from chronic diseases[116].

Recent research has shown that epigenetic regulators are highly involved with T cells, with both immune responses and disease development being possible outcomes of this relationship[117]. EZH2, a histone methyltransferase that methylates H3K27, has been identified as the most important factor in the differentiation of T-helper cells[107,116]. In this context, the deletion of EZH2 in antigen-specific CD4+ T cells prevents their differentiation into T-follicle helper cells, thus bringing to bear the critical role of EZH2 in this lineage establishment[105]. Mechanistically, they control the availability of chromatin at genes such as Bcl-6 and IL-21, which are required for Tfh cell development and function[117]. The altered differentiation of Tfh cells is the result of the action of EZH2 and DNMT1, a DNA methyltransferase, which secretes chemokines in the TME[118]. Researchers have shown in ovarian cancer models that both EZH2 and DNMT1 suppress the production of CXCL9 and CXCL10, two important Th1-attracting chemokines, as they are responsible for attracting immune cells to the tumour[118].

The RUNX family of transcription factors, particularly RUNX3, contributes to the complexity of epigenetic regulation in T-cell development by silencing the *CD4* gene during CD8+ T-cell lineage formation[119]. The analyses of the RUNX1 and RUNX3 interactome in thymoma cells with active CD4 silencing indicated the strong presence of G9a, a histone methyltransferase bound to the H3K9 site, mainly in the RUNX3 interactome[119]. This interaction suggests that G9a may be directed by RUNX3 to the *CD4* gene locus and consequently methylate histones[119]. Indeed, silencing of a silencer element or disruption of RUNX binding sites, which is the major silencing element, leads to continuous expression of the *CD4* gene in developing CD8+ T cells[119]. An interesting observation is that while RUNX3 is crucial for the initial suppression of CD4, its knockout in already differentiated CD8+ T cells does not cause reactivation of CD4, demonstrating that different mechanisms support the lack of CD4 silencing in mature cells[119]. Further exploration of the intricate interplay between epigenetic modifiers and transcription factors will be critical to understand T-cell development, their function, and their impact on immunologic diseases[119].

7. Inhibitors of Histone Methyl Transferases

Inhibitors of histone methyltransferases are needed to prevent aberrant methylation processes leading to pathogenesis and to control disease conditions. Small molecule compounds that can precisely modify histone methyltransferases and methylation reader proteins have been developed in the hope of developing viable therapeutic drugs[120]. One such result of the aberrant methylation process is due to the H3K4 mutations that lead to the translocation of the MLL1 protein. H3K4 trimethylation (H3k4me3) was higher in *CD274* promoter regions in pancreatic cells[121]. MLL1 directly binds to the *cd274* promoter and catalyses H3K4me3 to activate PD-L1 transcription in tumour cells[121]. MS132 selectively inhibits the von Hippel–Lindau (VHL)-recruiting WDR5 degrader, which inhibits the proliferation of PDAC cells[122].

Several inhibitors of an important HKMT, EZH2 have been developed, namely UNC-1999, EPZ-011989, GSK926, EPZ-005687, GSK343, EPZ-6438, CPI-169, GSK126, EI-1, EPZ005687. CPI-169 (NCT02395601), GSK126 (NCT02082977), and EPZ-6438 (tazemetostat-NCT01897571, NCT02601950, NCT02601937) have already entered clinical trials, but 3-DZNeP, as a potent EZH2 inhibitor, has not yet passed clinical testing as its pharmacokinetic properties have not yet been elucidated[123,124]. Chaetocin is known to reduce the radioresistance of lung cancer (NSCLC) cell lines (H460 and H1299) and tends to decrease the administered radiation dose in both cell lines. This effect was attributed to chromatin condensation (also referred to as chaetocin-induced chromatin condensation, CICC) in H1299 cells alone. Moreover, the effect was reversible when HKMTs, SUV39H1 and G9a were re-expressed. Thus, it can be concluded that chaetocin acts as a natural inhibitor of HKMTs in lung cancer[68,125].

Several inhibitors of histone methyltransferase variants (H3K79, H3K4 and H3K27, H3K9, H3K36, H3K20) have been synthesised and are listed in Table 1.

Table 1. List of several inhibitors of histone methyltransferases

Subunit	Target	Inhibitor	IC50	Action	References
H3K79	**Dot1L**	EPZ004777 (mimic of S-adenosylmethionine, SAM)	0.4 nM	Structurally binds and blocks DOT1L and inhibits H3K79 methylation, and blocks the expression of leukemogenic genes in MLL	24
		SGC0946	0.3 nM	8-fold higher potency than EPZ004777	25
		Pinometostat		Pinometostat decreased the levels of H3K79me2 at loci HOXA9, MEIS1, as well as HOXA9 inhibition in some PBMCs samples	87
H3K27	**EZH1/2**	3-deazaneplanocin A (DZNep)	-	SAH hydrolase inhibition, which in turn decreases cellular levels of PRC2 components, thereby inhibiting EZH2 inhibition	28
		EPZ005687	54 nM	Deplete global H3K27me3 levels, in EZH2-containing PRC2	44
		GSK126	9.9 nM		45
		EI1	15 nM		46
		GSK343	174 ± 84 nM	Competitive inhibitor of SAM	126
		PF-06821497	4 nM	Blocks EZH2 binding pocket	127
		Tazemetostat (EPZ6438)	2–38 nM	SAM competitive inhibitor	123
		CPI-1205	52 ± 11 nM (EZH1) 0.002 μM (EZH2)	SAM competitive inhibitor	128
		DS-3201	<=10 nM	SAM competitive inhibitor	129
		SAH-EZH2		Targets EED and disrupts EZH1/EZH2–EED complex	130
		A-395	18 ± 2 nM	Allosteric antagonist of PRC2	131
		EED226	23.4 nM	Allosteric antagonist of PRC2	132
H3K9	**SUV39H1**	**Chaetocin**	0.8 μM	Inhibits SUV39H1 in a SAM competitive manner.	47
	G9a	**PS-ETP1**	5.2 μM		48
		BIX-01294	1.7 μM	Substrate competitive inhibition in G9a by competing with its closely related GLP SET domain	49
		E72	-	Mimic the K9 side chain of H3, thereby acting as an effective inhibitor	50
		UNC0321	Ki= 63 pM	An extended 7-amino alkoxy side chain occupies the G9a lysine-binding site	53,133
		UNC0638	<2.5 nM	High potency and specificity for G9a and low toxicity, poor pharmacokinetics	61
		UNC0642	<2.5 nM	Same as UNC0638 but with improved pharmacokinetics	63
		BRD4770	EC50 = ~50 μM	SAM inhibitor	54
H3K36	**SMYD2**	AZ505	0.12 μM	Peptide competitive inhibition of SMYD2 by binding in the P53-binding pocket	55
		BAY-598	58 nM	Substrate competitive inhibitor	88
		LLY-507	<1 μM	Substrate competitive inhibitor	89
	SETD2	N-propyl-modified sinefungin (Pr-SNF)	-	Competitive inhibitor of SETD2 by occupying the SAH-binding pocket	56
H4K20	**SETD8**	Nahuoic acid A	6.5 μM	Competitive inhibitor of SETD8 by competing with SAM binding	57

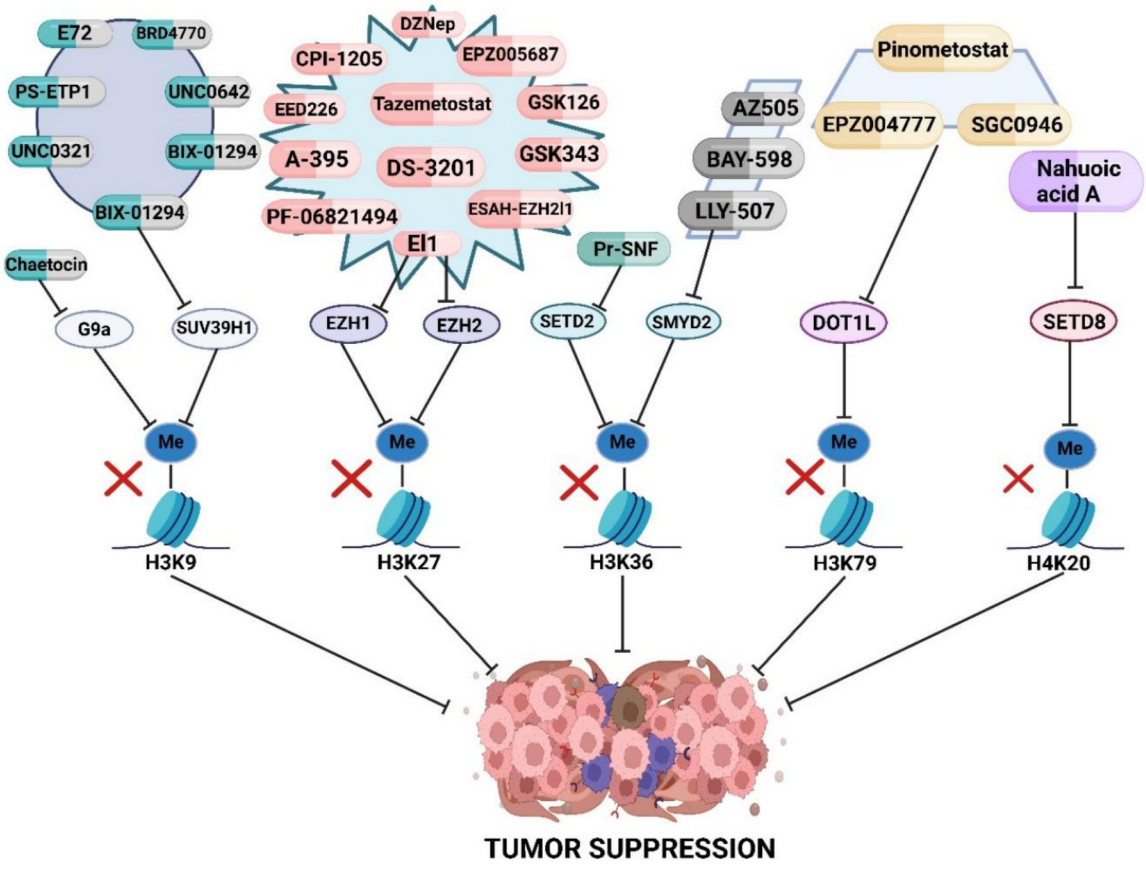


Figure 4. Various inhibitors of HKMTs that act on histone subunits to suppress tumour progression.

Most of the inhibitory molecules are known to block the binding pocket of S-adenosylmethionine, resulting in deactivation of enzymatic activity (Figure 4).

8. Inhibitor Design

In recent years, several crystal structures of histone lysine and arginine methyltransferase in association with the cofactor analogue SAH and/or with peptide substrates have been published[134-136]. However, no 3D structure of a complex of a histone methyltransferase and an inhibitor has yet been discovered. To understand the structural requirements for the binding of an inhibitor, a series of molecular modelling and docking studies for histone methyltransferases has been carried out due to the limited number of experimental structures. Zhang and Cheng put forward the first analytical study of an enzyme-substrate interaction by analysing the crystal structure of rat PRMT1 and SAH with a substrate peptide[137]. The result was that two active sites (Glu 144 and Glu 153) are responsible for the enzymatic activity and that dimerisation of PRMT1 is required for cofactor binding. This was also demonstrated by the fact that PRMT1 was maintained at an unfavoured pH, resulting in a conformational change of Glu153 (active site) and a disordered α-helix[66,67,138].

The antiviral, anticancer, and antibacterial properties of Schiff base complexes containing the oxime (–C N–OH) functional group have attracted attention. Benzamide oxime is used as a building block in drug development. The hydrogen bonding systems in the crystal structures of oximes have been studied, and a link between the hydrogen bonding patterns and the lengths of the Nitrogen–Oxygen bonds has been proposed. Oxime is used as an intermediate in the commercial production of caprolactam (precursor of Nylon 6). Antidotes for neurotoxins are oxime chemicals. Pralidoxime (also known as 2-PAM), obidoxime, methoxime, HI-6, Hlo-7, and TMB-4 are the most effective antidotes for neurotoxins. The success of oxime therapy depends on the nerve agent used[139]. A study has shown that the compounds obtained by oximation of (E)-3-aryl-6,7-dihydrobenzisoxazol-4(5H)-ones and subsequent *O*-acylation with acylamidobenzoic

acids exhibit antiproliferative activity on breast cancer cell lines[140]. Structure-activity relationship analysis of several psammaplin A derivatives has shown that oxime functionality confers high selectivity to these compounds against HDACs, specifically HDAC1[141]. Added 4-oxime derivatives have also shown high selectivity against HDAC6 and HDAC8[142].

9. Conclusions

Histone methyl transferases play different roles in various pathologies. It is not certain that the roles played by one set of HKMTs in a particular disease may have the same molecular mechanisms in another disease. Conserved regions of histone methyltransferases and regions in the histone subunit are specific and critical for the development and molecular changes in cancer and other diseases. Due to their specificity and reversible nature as epigenetic regulators, several inhibitors against histone lysine methyltransferases have been developed and are in clinical trials, most of them being promising therapeutic agents. In clinical trials, HMT inhibitors have shown promising anti-tumour efficacy as single or multidrug treatments in certain tumour types and mutational backgrounds, and in some cases have extended life expectancy with fewer adverse effects than traditional chemotherapy. However, the molecular mechanisms underlying the action of certain drugs and their pharmacokinetic properties are still being evaluated and also pose obstacles to successful clinical outcomes. In addition, the long-term consequences of such drugs are uncertain, and people exposed to them should be monitored more closely.

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11. References

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