Histone-Lysine *N*-Methyltransferase 2D (KMT2D) Impending Therapeutic Target for the Management of Cancer: The Giant Rats Tail

Meshak Dhanashekaran Cecileya Jasmin,[a,b] Narayanaswamy Radhakrishnan,[a,*] Venugopal Vinod Prabhu,[c] Kunnathur Murugesan Sakthivel,[d] & Rasmi Rajan Radha[e]

[a]Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Thandalam, Chennai, Tamil Nadu 602105, India; [b]Department of Biochemistry, Tagore Medical College and Hospital, Rathinamangalam, Melakottaiyur, Chennai, Tamil Nadu 600127, India; [c]PG Department of Microbiology, PERI College of Arts and Science, Tambaram, Mannivakkam, Chennai, Tamil Nadu 600048, India; [d]Department of Biochemistry, PSG College of Arts & Science, Coimbatore, Tamil Nadu 614014, India; [e]Department of Biotechnology, PSG College of Arts & Science, Coimbatore, Tamil Nadu 614014, India

*Address all correspondence to: Dr. Narayanaswamy Radhakrishnan, Professor, Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Thandalam, Chennai, Tamil Nadu- 602105, India; Tel.: +91 7305327126, E-mail: nrkishnanr@gmail.com

ABSTRACT: The histone-lysine *N*-methyltransferase 2D (KMT2D), tumor suppressor gene which is the major component of histone H3K4 mono-methyltransferase in mammals and has significant role in regulation of a gene which are frequently mutated that lead to many different types of cancers that include non-Hodgkin lymphoma, medulloblastoma, prostate carcinoma, renal carcinoma, bladder carcinoma and lung carcinoma. KMT2D gene epigenetic alterations in histone methylation play a significant role for the initiation and progression of cancers from pre-cancerous lesions, yet its complete function in oncogenesis remains unsolved. KMT2D deficiency - loss are thought of initial mediators of cancer development and cell migration such as B-cell lymphoma, medulloblastoma, melanoma, pancreas and lung cancer. The KMT2D loss has know to activate glycolytic genes that promote aggressive tumor progression. Therefore, the present review serves to underline the update on recent research pertaining to KMT2D gene, that could be a potential therapeutic target in downregulating glycolytic genes such as Pgk1, Ldha, Pgam1 and Gapdh; 2, epidermal growth factor receptor tyrosine kinase (EGFR-TK) - ERBB2, RTK-RAS signaling, RAS activator genes Rgl1, Rasgrp1, Rasgrf1, Rasgrf2 and Rapgef5 in suppressing the tumor progression that may represent novel targeted therapy for the management of cancer. This review will facilitate to understand the gene expression that inhibits cancer progression and which could serve as a potential molecular target in understanding cancer pathogenesis.

KEY WORDS: KMT2D, lung cancer, methyltransferase, tumor suppressor gene

I. INTRODUCTION

Histone-lysine *N*-methyltransferase 2D (KMT2D), histone H3K4 mono-methyltransferase in mammals located at chromosome region 12q13.12, which has an significant role in gene regulation, development of diseases and promotes cancer development.[1] H3K4 (methyl group on histone H3 lysine 4 residue) where the cells active promoters and enhancer are marked by tri-methylation H3K4 and mono- and di-methylation of H3K4 respectively.[2] In mammals there are six sets of H3K4 methyltransferases such as KMT2A, KMT2B, KMT2C, KMT2D, KMT2F and KMT2G.[1] Sequence homology studies of SET-containing enzymatic subunits have demonstrated that KMT2C and KMT2D are homologous to Trr (trithorax related), KMT2A and KMT2B are homologous to Trx and KMT2F and KMT2G are homologous to dSet1.[3] KMT2D have significant role in regulation of the gene which are frequently mutated that lead to cancer progression.[1] Epigenetic alterations of KMT2D histone methylation and acetylation are important for the initiation and progression of cancers from pre-cancerous lesions.[4] KMT2D are an predominant elements on enhancer regions and has limited efficient redundancy with KMT2C which has been proved in human colon cancer cell line HCT 116 cells.[4] KMT2D is also known to binds to specific enhancer region selectively that depends on the cell stage of

0731-8898/25/$35.00

differentiation with the help of TFs and the early adipogenic TF CCAAT/enhancer-binding protein β (C/EBPβ).[5] KMT2D gene has direct function in the development, differentiation and tumor suppression through TFp53 (tumor protein p53).[6] It was reported that KMT2D act as co activators of TFp53 which are crucial for the gene expression of p53 target genes in response to doxorubicin drug which are DNA damaging agents.[6] It has been well documented that KMT2D could be a potent tumor suppressor function as the animal study demonstrated, the crossed KMT2D conditional KO mice ($Kmt2d^{f/f}$) in $CD19^{+}$ early B cells developed highly proliferative B cell lymphomas.[7] The KMT2D mutations are resulted from premature stop codons, frame shift insertions and splice-site mutations that generated truncated proteins products that are deficient in part of the C-terminal protein domains.[8] The authors reported that monoallelic truncating mutations of KMT2D are also important causative agents of rare congenital disease of Kabuki syndrome.[9] KMT2D deficiency is the part of initiator forces for the initiation, cell migration and development of cancers such as B-cell lymphoma, medulloblastoma, melanoma, pancreas and lung cancer. Therefore this review could assist to understand the regulation of gene expression that inhibit cancer progression and serve as potential molecular target in cancer pathogenesis.

II. KMT2D DEFICIENCY AND KMT2D LOSS PROMOTES CANCER PROGRESSION

KMT2D deficiency has been determined and documented through the measurement of proliferation of KMT2D-deficient cells. A research study with $KMT2D^{+/-}$ isogenic cell lines showed compromised ability of $KMT2D^{+/-}$ cells to form colonies. Furthermore the KMT2D deficiency attenuates cell migration since KMT2D-regulates genes that have shown to be linked to cancer cell migration and formation of extracellular matrices by transwell assay.[10,11]

The loss of function mutations have been known to be a part of a striking forces for the progression of many cancers like B-cell lymphoma, medulloblastoma, melanoma and lung cancers.[12] The study reveals, the loss of KMT2D function could alter the H3K4 methylation *in vivo* as the authors explained with splenic $B220^{+}$ and germinal center (GC) B cells derived and purified from mice in which the KMT2D gene had been conditionally deleted via Cre-mediated recombination. They documented that, compared to wild-type KMT2D-deficient B cells has showed low levels expression of H3K4me1, H3K4me2 and H3K4me3. Therefore the study proved that KMT2D functions as a non-redundant methyltransferase that controls, methylation state.[10,11]

The study examined KMT2D deficiency in breast and colon cancer cell and the author reported that KMT2D deficiency promotes arrest in the cancer cell proliferation.[11] Guo et al. (2013) documented the knockdown of KMT2D resulted in declined cancer cell proliferation in HeLa cells. Somatic gene knockout approaches have been successful in generating a panel of isogenic KMT2D-deficient cancer cell lines which was designed to study KMT2D deficiency in neoplastic cells. The heterozygous KMT2D mutant-harboring cell lines are known as KMT2D-deficient ($KMT2D^{+/-}$). The authors conclude the biological role of KMT2D subsequently by measuring the proliferation of KMT2D-deficient cells compared to parent $KMT2D^{+/-}$ isogenic cell lines. The author further reveals that slower proliferation rate of $KMT2D^{+/-}$cells to form colonies in the experimental well plate's assay.[11]

KMT2D deficiency has been shown to upregulate ribosome biogenesis in human AML.[12] The authors substantiate the role of KMT2D deficiency that upregulates the ribosome biogenesis in KMT2D deficient leukemia cells. As transcriptomic profiles of 142 AML patients in the TCGA-LAML cohort was studied and it was reported that upregulated genes in KMT2D low expression AML patients was highly positively enriched in GO_ribosome_biogenesis.[12] KMT2D deficient acute myeloid leukemia (AML) cells are sensitive to the inhibitor of ribosome biogenesis as the experimental mice bearing shKmt2d AML with CX-5461 (an inhibitor of rRNA synthesis). CX-5461 targets DNA polymerase 1 (Pol I) -mediated transcription. The treatment with CX-5461 increases the life span of the experimental animals which are transplanted with shKmt2d AML cells. Also the study reported that in CX-5461-treated animals, there was a significant reduction

in the shKmt2d leukemia cells in the treated animals' peripheral blood.[12–15] The authors prove that CX-5461 is an efficient drug for treating Kmt2d-deficient AML (ribosome biogenesis).[7]

III. KMT2D AS MOLECULAR TARGET FOR THE MANAGEMENT OF CANCER

In human lung cancer, KMT2D alterations frequently co-occur with alterations in the mutated genes71% TP53 and 22% KRAS thus lung-specific loss of KMT2D cooperates with Trp53 inactivation or KRAS activation for lung tumorigenesis in mice.[13] The author reveals the lung-specific loss of Kmt2d promoted KRAS-induced lung tumorigenesis (high pulmonary parenchyma in KRAS;Kmt2d$^{-/-}$ tumor animals). The cell proliferation marker Ki-67 was also increased due to KMT2D loss and shortened the life survival of the experimental animals with KRAS pulmonary tumors. Thus the author concludes that KMT2D loss, like Trp53 loss, initiates lung squamous cell carcinoma and lung adenocarcinoma (LUAD) tumorigenesis.[13]

Interestingly the increased glycolysis in KMT2D-defective lung cancer cells could be targeted by small molecule inhibition since the KMT2D acts as an epigenetic LUAD suppressor by positively regulating super-enhancers (Per2 super-enhancer) thus increased the expression of tumor suppressor gene Per2.[13] In KMT2D deficiency, the decrease in Per2 expression to upregulate glycolytic genes such as ENO1, PGK1, PGAM1, LDHA and CDK1 thus the author conclude that tumor-suppressive function of KMT2D is dependent, at least in part, on the downregulation of glycolytic genes by Per2 and Per3.[13]

In another study, the author reported that KMT2D (lysine methyltransferase 2D) loss leads to enhancer reprogramming on tumor suppressor genes including insulin like growth factor binding protein 5- IGFBP5 that have important role in insulin growth factor receptor -1 signaling pathway (serine/threonine kinase AKT) for regulating glucose and lipid energy metabolism.[14]

Cancer cells are dependent on the glycolysis pathway since they act as a central node for rapid proliferating cells for the aggressive tumor progression.[14] These study results implicate glycolysis inhibition as a potential target in patients with melanoma.[14] Further, it is well understood that KMT2D loss, upregulated the expression of tumor-promoting glycolytic genes, such as Eno1, Pgk1, Pgam1, Ldha and Gapdh; 2.[13,14] KMT2D loss upregulate glycolysis via IGFBP5-regulated IGF signaling while promoting melanoma tumorigenesis.[15] Further the above findings provides an valuable role for a better targeted for lung cancer which is also substantiated by the development of medulloblastoma in brain-specific KMT2D knockout mice, and Kmt2d loss induces Ras signaling pathways, increasing expression of Ras activator genes such as Rgl1,and other Ras mediated genes.[16]

In an experimental study the KMT2D loss, increased the activation of receptor tyrosine kinases (RTKs).[17] The study reveals that KMT2D loss lead to increase in the KRAS signaling and EGFR phosphorylation in lung squamous cell carcinoma (LUSC).[17] Thus deletion or loss of KMT2D could promote oncogenic RTK-RAS signaling through activating EGFR and ERBB2 in both murine and human LUSC.[14] The study further analyzed to target KMT2D through signaling pathway. The data ensure that the SHP099 or afatinib alone or in combination inhibits RTK-RAS signaling in KMT2D KO LUSC. Treating KMT2D KO LUSC cells *in vitro* with SHP099 or afatinib alone strongly reduced phospho-ERK (pERK) levels significantly thus combination therapy led to downregulated tumorprogression.[17] KMT2D loss leads to decrease the expression of receptor type protein tyrosine phosphatases (RPTPs), which in turn activate oncogenic RTK-RAS signaling to promote tumorigenesis in LUSC. The study substantiate that KMT2D loss promotes activation of EGFR and ERBB2, due to the repressed RPTP expression leads to the potentiating of RTK-RAS signaling thus promote tumor growth in LUSC. The study targets KMT2D-deficient LUSC with SHP2 and pan-ERBB inhibitors thus reduces LUSC oncogenesis to enable potential therapeutic property. The authors conclude that SHP099 and afatinib possessed superior antitumor effect with decrease of tumor volumes in LK2, a human LUSC cell line with a KMT2D nonsense mutation.[17]

IV. KMT2D MUTATION IN LUNG CARCINOMA

KMT2D having the greatest prevalence of alterations. Missense mutations, nonsense mutations, silent mutations, frame shift insertions and deletion and in-frame

deletions are reported in cancers such as intestine cancer, skin cancer, and stomach cancer. KMT2D, 48.7% were truncating mutations, which was reported to be the highest of all the epigenetic modifiers examined so far.[13] Epigenetic alterations in histone methylation have a significant role for the cancer initiation, progression from precancerous lesions to invasive cancer progression.[17,21] KMT2D altered mutation has been observed in many cancers, including non-Hodgkin lymphoma (9.96%), medulloblastoma (15.62%), and pancreatic carcinoma (6.1%), renal solid tumor (10.18%), bladder (29.07%), glioblastoma (8.13%), breast carcinoma (5.79%), ovarian carcinoma (7.25%) and in lung carcinoma – non small cell lung cancer (NSCLC) (10.11%).[17–21] Histone methylation modifiers and other epigenetic modifiers was also reported to be often mutated in lung adenocarcinoma 40%–50% in LUAD and lung squamous cell carcinoma 25%–30% lung adenocarcinoma and lung squamous cell carcinoma (LUSC) respectively although only limited research study on KMT2D mutations on lung cancer are existed.[13] KMT2D, gene whose mutation are associated with significantly abridge the survival in NSCLC and KMT2D mutation was more common in women.[18] The author identifies 41 mutations of KMT2D from the 34 tumor samples and majority was missense mutations with multiple missense mutations (A2925V, A4425V, L2245V) in a single tumor was identified and reported.[18] The study reveals that 30 mutations of KMT2D in 21 tumor samples and the majority were the missence mutation similar to NSCLC. It was interestingly to know the KMT2D function as tumor suppressor which get mutated among the lung cancer patients, other 44 genes that are co-mutated along with KMT2D genes (AKT3, CCND2, KEAP1, NF1, and BRAF)[18] The research further reveals that KMT2D alterations frequently co-occur with mutated genes TP53 and KRAS in human lung cancer.[18] The study further reveals that around 71% of KMT2D alterations co-occur with TP53 alterations in lung tumors and about 22% of KMT2D alterations with KRAS alterations among LUAD.

The KMT2D loss upregulated glycolysis to promote aggressive growth of human lung cancer cells, therefore inhibition of glycolysis that could be a better target to impede the lung cancer cell growth.[15] The study tested with multiple inhibitors among human LUAD cells and human LUAD cell lines bearing KMT2D-truncating mutations (H1568, with a nonsense mutation E758; DV-90. The author reported that glucose uptake, lactate excretion, and glycolysis was higher in the KMT2D-mutant cell lines then KMT2D-WT cell lines.[13] The study further reveals that 2-deoxy-D-glucose (2-DG), a hexokinase inhibitor and POMHEX, an enolase inhibitor agents inhibited the confluency of the KMT2D-mutant cell lines to a significant extent then compared with KMT2D-WT cell lines thus increased in the glycolysis in KMT2D-mutant LUAD tumors could be potentially targeted by the glycolysis inhibitor 2-DG in lung cancer.[13,22] Taken together, KMT2D mutation status could deserve its own separate molecular classification in NSCLC as it is an emerging therapeutic potential of targeting epigenetic modifiers in cancer.

V. CONCLUSION

Together, in this review, there exist significant records to substantiated the functional and molecular role of KMT2D a tumor suppressor gene, expression system in a different cancer models and these study propose that targeting KMT2D could be a potential therapeutic target in downregulating signaling pathways and glycolysis in suppressing the tumor progression that could be a novel therapeutic target for the treatment of cancers. Further investigation are necessary to understand the key role of KMT2D as tumor suppressor and targeting KMT2D in cancer cells for its role in cell signaling and glycolytic pathway for the suppression of tumor progression across a range of cancers. This review will facilitate to understand the gene expression and gene products that inhibits cancer progression and could be a potential molecular target in preventing cancer deaths.

ACKNOWLEDGMENTS

The valuable support of Head, Dept of Biochemistry and the Management of SIMATS, is greatly acknowledged.

REFERENCES

1. Pan Y, Han H, Hu H, Wang H, Song Y, Hao Y, Tong X,

Patel AS, Misirlioglu S, Tang S, Huang HY, Geng K, Chen T, Karatza A, Sherman F, Labbe KE, Yang F, Chafitz A, Peng C, Guo C, Moreira AL, Velcheti V, Lau SCM, Sui P, Chen H, Diehl JA, Rustgi AK, Bass AJ, Poirier JT, Zhang X, Ji H, Zhang H, Wong KK. KMT2D deficiency drives lung squamous cell carcinoma and hypersensitivity to RTK-RAS inhibition. Cancer Cell. 2023;41(1):88–105.e8.

2. Calo E and Wysocka. Modification of enhancer chromatin: What, how, and why? J Mol Cell. 2013;49(5):825–37.
3. Shilatifard A. The COMPASS family of histone H3K4 methylases: Mechanisms of regulation in development and disease pathogenesis. Annu Rev Biochem. 2012;81:65–95.
4. Ardeshir-Larijani F, Bhateja P, Lipka MB, Sharma N, Fu P, Dowlati A. KMT2D mutation is associated with poor prognosis in non-small-cell lung cancer. Clin Lung Cancer. 2018;19(4):e489–e501.
5. Lee JE, Wang C, Xu S, Cho YW, Wang L, Feng X, Baldridge A, Sartorelli V, Zhuang L, Peng W, Ge K. H3K4 mono- and di-methyltransferase MLL4 is required for enhancer activation during cell differentiation. Elife. 2013;2:e01503.
6. Lee J, Kim DH, Lee S, Yang QH, Lee DK, Lee SK, Roeder RG, Lee JW. A tumor suppressive coactivator complex of p53 containing ASC-2 and histone H3-lysine-4 methyltransferase MLL3 or its paralogue MLL4. Proc Natl Acad Sci. 2009;106:8513–8.
7. Ortega-Molina A, Boss IW, Canela A, Pan H, Jiang Y, Zhao C, Jiang M, Hu D, Agirre X, Niesvizky I, Lee JE, Chen HT, Ennishi D, Scott DW, Mottok A, Hother C, Liu S, Cao XJ, Tam W, Shaknovich R, Garcia BA, Gascoyne RD, Ge K, Shilatifard A, Elemento O, Nussenzweig A, Melnick AM, Wendel HG. The histone lysine methyltransferase KMT2D sustains a gene expression program that represses B cell lymphoma development. Nat Med. 2015;21(10):1199–208.
8. Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, Johnson NA, Severson TM, Chiu R, Field M, Jackman S, Krzywinski M, Scott DW, Trinh DL, Tamura-Wells J, Li S, Firme MR, Rogic S, Griffith M, Chan S, Yakovenko O, Meyer IM, Zhao EY, Smailus D, Moksa M, Chittaranjan S, Rimsza L, Brooks-Wilson A, Spinelli JJ, Ben-Neriah S, Meissner B, Woolcock B, Boyle M, McDonald H, Tam A, Zhao Y, Delaney A, Zeng T, Tse K, Butterfield Y, Birol I, Holt R, Schein J, Horsman DE, Moore R, Jones SJ, Connors JM, Hirst M, Gascoyne RD, Marra MA. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature. 2011;476(7360):298–303.
9. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura K, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ, Shendure J. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010;42(9):790–3.
10. Guo C, Chang CC, Wortham M, Chen LH, Kernagis DN, Qin X, Cho YW, Chi JT, Grant GA, McLendon RE, Yan H, Ge K, Papadopoulos N, Bigner DD, He Y. Global identification of MLL2-targeted loci reveals MLL2's role in diverse signaling pathways. Proc Natl Acad Sci U S A. 2012;109(43):17603–8.
11. Guo C, Chen LH, Huang Y, Chang CC, Wang P, Pirozzi CJ, Qin X, Bao X, Greer PK, McLendon RE, Yan H, Keir ST, Bigner DD, He Y. KMT2D maintains neoplastic cell proliferation and global histone H3 lysine 4 monomethylation. Oncotarget. 2013;4(11):2144–53.
12. Xu J, Zhong A, Zhang S, Chen M, Zhang L, Hang X, Zheng J, Wu B, Deng X, Pan X, Wang Z, Qi L, Shi K, Li S, Wang Y, Wang M, Chen X, Zhang Q, Liu P, Gale RP, Chen C, Liu Y, Niu T. KMT2D deficiency promotes myeloid leukemias which is vulnerable to ribosome biogenesis inhibition. Adv Sci. 2023;10(19):e2206098.
13. Alam H, Tang M, Maitituoheti M, Dhar SS, Kumar M, Han CY, Ambati CR, Amin SB, Gu B, Chen TY, Lin YH, Chen J, Muller FL, Putluri N, Flores ER, DeMayo FJ, Baseler L, Rai K, Lee MG. KMT2D deficiency impairs super-enhancers to confer a glycolytic vulnerability in lung cancer. Cancer Cell. 2020;37(4):599–617.e7.
14. Murugesan N, Maitituoheti M. KMT2D deficiency confers a therapeutic vulnerability to glycolytic and IGFR inhibitors in melanoma. Mol Cell Oncol. 2021;8(5):1984827.
15. Maitituoheti M, Keung EZ, Tang M, Yan L, Alam H, Han G, Singh AK, Raman AT, Terranova C, Sarkar S, Orouji E, Amin SB, Sharma S, Williams M, Samant NS, Dfhamdhere M, Zheng N, Shah T, Shah A, Axelrad JB, Anvar NE, Lin YH, Jiang S, Chang EQ, Ingram DR, Wang WL, Lazar A, Lee MG, Muller F, Wang L, Ying H, Rai K. Enhancer reprogramming confers dependence on glycolysis and IGF signaling in KMT2D mutant melanoma. Cell Rep. 2020;33(3):108293.
16. Dhar SS, Zhao D, Lin T, Gu B, Pal K, Wu SJ, Alam H, Lv J, Yun K, Gopalakrishnan V, Flores ER, Northcott PA, Rajaram V, Li W, Shilatifard A, Sillitoe RV, Chen K, Lee MG. MLL4 is required to maintain broad H3K4me3 peaks and super-enhancers at tumor suppressor genes. Mol Cell. 2018;70(5):825–41.e6.
17. Pan Y, Han H, Hu H, Wang H, Song Y, Hao Y, Tong X, Patel AS, Misirlioglu S, Tang S, Huang HY, Geng K, Chen T, Karatza A, Sherman F, Labbe KE, Yang F, Chafitz A, Peng C, Guo C, Moreira AL, Velcheti V, Lau SCM, Sui P, Chen H, Diehl JA, Rustgi AK, Bass AJ, Poirier JT, Zhang X, Ji H, Zhang H, Wong KK. KMT2D deficiency drives lung squamous cell carcinoma and hypersensitivity to RTK-RAS inhibition. Cancer Cell. 2023;41(1):88–105.e8.
18. Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, Johnson NA, Severson TM, Chiu R, Field M, Jackman S, Krzywinski M, Scott DW, Trinh DL, Tamura-Wells J, Li S, Firme MR, Rogic S, Griffith M, Chan S, Yakovenko O, Meyer IM, Zhao EY, Smailus

D, Moksa M, Chittaranjan S, Rimsza L, Brooks-Wilson A, Spinelli JJ, Ben-Neriah S, Meissner B, Woolcock B, Boyle M, McDonald H, Tam A, Zhao Y, Delaney A, Zeng T, Tse K, Butterfield Y, Birol I, Holt R, Schein J, Horsman DE, Moore R, Jones SJ, Connors JM, Hirst M, Gascoyne RD, Marra MA. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature. 2011;476(7360):298–303.

19. Dalgliesh GL, Furge K, Greenman C, Chen L, Bignell G, Butler A, Davies H, Edkins S, Hardy C, Latimer C, Teague J, Andrews J, Barthorpe S, Beare D, Buck G, Campbell PJ, Forbes S, Jia M, Jones D, Knott H, Kok CY, Lau KW, Leroy C, Lin ML, McBride DJ, Maddison M, Maguire S, McLay K, Menzies A, Mironenko T, Mulderrig L, Mudie L, O'Meara S, Pleasance E, Rajasingham A, Shepherd R, Smith R, Stebbings L, Stephens P, Tang G, Tarpey PS, Turrell K, Dykema KJ, Khoo SK, Petillo D, Wondergem B, Anema J, Kahnoski RJ, Teh BT, Stratton MR, Futreal PA. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature. 2010;463(7279):360–3.
20. Yang Z, Li C, Fan Z, Liu H, Zhang X, Cai Z, Xu L, Luo J, Huang Y, He L, Liu C, Wu S. Single-cell sequencing reveals variants in ARID1A, GPRC5A and MLL2 driving self-renewal of human bladder cancer stem cells. Eur Urol. 2017;71(1):8–12.
21. Rohilla S, Singh M, Alzarea SI, Almalki WH, Al-Abbasi FA, Kazmi I, Afzal O, Altamimi ASA, Singh SK, Chellappan DK, Dua K, Gupta G. Recent developments and challenges in molecular-targeted therapy of non-small-cell lung cancer. J Environ Pathol Toxicol Oncol. 2023;42(1):27–50.
22. Alam H, Tang M, Maitituoheti M, Dhar SS, Kumar M, Han CY, Ambati CR, Amin SB, Gu B, Chen TY, Lin YH, Chen J, Muller FL, Putluri N, Flores ER, DeMayo FJ, Baseler L, Rai K, Lee MG. KMT2D deficiency impairs super-enhancers to confer a glycolytic vulnerability in lung cancer. Cancer Cell. 2020;37(4):599–617.e7.