[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Review Article

Dissecting the Functional Pleiotropism of Lysine Demethylase 5B in Physiology and Pathology

Oluwaseun Adebayo Bamodu[1,2]*, Tsu-Yi Chao[1,3,4]*

[1]Department of Hematology and Oncology, Cancer Center, Taipei Medical University - Shuang Ho Hospital, New Taipei City, Taiwan
[2]Department of Medical Research and Education, Taipei Medical University - Shuang Ho Hospital, New Taipei City, Taiwan
[3]Graduate Institute of Clinical Medicine, School of Medicine, Taipei Medical University, Taipei City, Taiwan
[4]Taipei Cancer Center, Taipei Medical University, Taipei City, Taiwan

Abstract

Background: The last two decades has been characterized by accruing evidence of the translational relevance of chromatin modification in normal genomic function, regulation, and pathology, especially with piqued interest in the intrinsic regulatory dynamism of histone methylation, and the increasing documentation of new members of the histone demethylase family. Recent studies provide functional and mechanistic insight into the peculiar biological role of these histone demethylases and their putative implication in pathological processes. **Objective:** This review aims to provide a summary of the latest findings related to pleiotropic roles of the Jumonji/AT-rich interactive domain (JARID) domain-containing lysine demethylase 5B (KDM5B, also known as JARID1B or PLU1) in physiology and pathology, with a focus on its therapeutic potentials. **Results:** KDM5B/JARID1B/PLU1 is restrictively expressed, evolutionarily conserved across mammalian species, and belonging to the α-ketoglutarate-dependent hydroxylase superfamily. KDM5B is actively involved in various physiological processes, including regulation of transcription elongation and alternative splicing in embryonic stem cells, epigenetic modulation of gene expression, neurogenesis, mammary gland development, and osteogenesis. Conversely, KDM5B is one of the earliest identified histone lysine demethylases associated with human disease, with several studies indicating that KDM5B plays a vital role in the initiation and progression of various malignancies, including lung, hypopharynx, brain, and breast cancers. **Conclusion:** This study provides concise insight into the functional pleiotropism of KDM5B in physiology and pathology, as well as highlights it role as an actionable therapeutic target.

Keywords: Cancer, epigenetics, histone demethylase, Jumonji AT-rich interactive domain 1B, lysine demethylase 5B, pathology, physiology

Introduction

Advances in genome-wide transcriptome analysis coupled with our increased knowledge of heritable phenotypes and the science underlying the same help inform our current

Received: 31-Dec-2019 **Revised:** 08-Feb-2020
Accepted: 20-Feb-2020 **Published:** 02-Jun-2020

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_5_20

Address for correspondence: Dr. Oluwaseun Adebayo Bamodu, Department of Hematology and Oncology, Cancer Center, Taipei Medical University - Shuang Ho Hospital, New Taipei City, Taiwan.
E-mail: 16625@s.tmu.edu.tw
Dr. Tsu-Yi Chao,
Taipei Cancer Center, Taipei Medical University, Taipei City, Taiwan.
E-mail: 10575@s.tmu.edu.tw

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: wkhlrpmedknow_reprints@wolterskluwer.com

How to cite this article: Bamodu OA, Chao TY. Dissecting the functional pleiotropism of lysine demethylase 5B in physiology and pathology. J Cancer Res Pract 2020;7:49-59.

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

understanding that alterations in the DNA nucleotide sequence are not always required for changes in heritable phenotypes.[1,2] This suggests a bio-phenomenon wherein heritable phenotypes may be associated with or initiated by bio-events "beyond, around, outside, on the top of, or in addition to" the well-established genetic alterations.[1-3] The study of this bio-phenomenon involving functionally-relevant alteration of the genome, gene expression, and/or activity, as well heritable phenotype, without changes in the genomic sequence, is herein termed epigenetics, and it antagonizes the sacrosanctity of the conventional genetic basis of inheritance.

Principal mechanisms underlying epigenetic activities include DNA methylation, histone modification, and RNA-related silencing, all of which are interrelated and inherently elicit changes in gene expression profile/pattern without altering the underlying DNA sequence.[4,5] Contextually, changes in gene expression/activity/behavior involve nongenetic factors, are mostly mediated by the activity of repressor proteins that bind to the DNA silencers, and are associated with epigenetic changes that last a cell's lifespan, or even over multiple cell generations, without altering the organisms' DNA sequence.[1-5] Of contextual-relevance to the present review is histone modification.

Histones are the principal protein components of the chromatin, a DNA–protein complex that constitutes chromosomes. Since histones are *de facto* spools around which the DNA molecules wind, modifications in histone structures after they are translated into protein, namely posttranslation modification, alter chromatin conformation, and this, in turn, determines or affects how the associated chromosomal DNA will be transcribed.[5-7] While the uncoiled or noncompact chromatin (forming a complex called euchromatin) is active and allows for the transcription of its associated DNA, the condensed or compact chromatin (forming a complex called heterochromatin) is inactive and precludes DNA transcription.[5-8]

Primarily, two main mechanisms underlie the modification of histones, namely acetylation and methylation, entailing the addition of either acetyl or methyl group (s), respectively, to the amino acid lysine in the histone. Conventionally, histone acetylation and deacetylation are associated with euchromatin (active) and heterochromatin (inactive), respectively, while methylation is associated with both the noncompact euchromatin and compact heterochromatin.[6-8] This is evidenced by the implication of histone H3 lysine 9 (H3K9) methylation in transcriptional repression/silencing and its role as a binding site for heterochromatin protein 1 (HP1), making it a mark of repressed DNA which is a characteristic of heterochromatin.[9,10] On the other hand, the methylation of H3K4 is associated with transcriptional activation of genes.[8,11-13]

The discovery and characterization of histone lysine demethylase 1A (KDM1A, also known as LSD1), which actively "erases" the methyl mark (s) from H3K4 through the enzymatic activity of its amine oxidase domain, complemented by the redox–active coenzyme flavin adenine dinucleotide, initiated a flurry of studies on the physiological and pathological implications of histone lysine demethylases (KDMs).[14] Subsequently, a broad family of related KDMs and their substrates has been and continues to be identified and characterized,[14-17] explaining the existence of matched KDMs for most methylated lysine residues of the histone tails, and reinforcing the nonsacrosanct nature of the initially proposed irreversibility of histone methylation. In fact, the last two decades has been characterized by accrued evidence of the critical, often essential, role of this dynamism in histone methylation regulation in "fundamental chromatin-based processes,[14] especially as impaired regulation of KDMs is increasingly implicated in a broad array of human diseases or disorders, including developmental disorders, mental retardation, and cancer.[14,17-21] These, among many other reasons, make KDMs emerging therapeutic targets.[21,22]

Lysine demethylase 5 (KDM5) enzymes are some of the most studied KDMs. Recently, it was demonstrated that the interaction and complex-formation between a plant homeodomain (PHD) in KDM5A/5B and unmodified H3K4 resulted in the induction of the KDM5s' enzymatic activity and methylation of H3K4 (H3K4me).[23,24] Moreover, another PHD finger in these KDM5s exhibits a preference for binding to H3K4me histone tails, in part indicating that KDM5s, and more specifically KDM5B, recognize both the substrate and the product of their demethylating enzymatic activity.[25] While "the functional relevance of this interplay remains to be carefully examined *in vivo*," this observation is suggestive of existent coordinated drive by KDMs to encrypt/conceal "domains that can read the chromatin modification landscape to control histone demethylation."[14]

The Jumonji/AT-rich interactive domain (ARID)-containing lysine demethylase 5B (KDM5B/JARID1B/PLU1) is restrictively expressed, evolutionarily conserved across mammalian species, and belonging to the α-ketoglutarate-dependent hydroxylase superfamily.[26] KDM5B is actively involved in various physiological processes, including regulation of transcription elongation and alternative splicing in embryonic stem (ES) cells,[27,28] epigenetic modulation of gene expression, neurogenesis,[29,30] mammary gland development,[31] and osteogenesis.[32] Conversely, KDM5B is one of the earliest identified histone KDMs associated with human disease, with several studies indicating that KDM5B plays a vital role in the initiation and progression of various malignancies, including lung,[33] hypopharynx,[34] brain,[35] and breast cancers.[36,37] This review aims to provide a summary of the latest findings related to the pleiotropic roles of KDM5B in physiology and pathology, with a focus on its therapeutic potentials.

Structure and Biogenesis of Lysine Demethylase 5B

KDM5B, a 1544 residue member "of the family of Jumonji C (JmjC) domain containing iron (Fe) and

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

α-ketoglutarate (α-KG)-dependent oxygenases,"[38] is located within the human chromosome 1 (chr 1): 202,724,495–202,809,470 (GRCh38/hg38) or chr 1: 202,696,526–202,778,598 (GRCh37/hg19) with 84,976 or 82,073 bases, respectively, on the 1q32.1 cytogenetic band (https://www.genecards.org/cgi-bin/carddisp.pl?gene=KDM5B&keywords = kdm5b) [Figure 1]. Structurally, KDM5B has seven identified domains, namely a catalytic JmjC domain, a JmjN domain, a DNA-binding ARID domain, three PHDs (PHD 1, 2, and 3), and a C_5HC_2 zinc finger, which form the KDM5B catalytic core.[38] Functional analyses indicate that the KDM5B ARID domain specifically recognizes and binds to the GCACA/C motif,[39] PHD1 binds H3K4me0 and H3K4me1,[25] PHD3 preferentially binds H3K4me3,[24] the JmjC domain forms a catalytically-active pocket that modulates Fe (III) and α-KG, which are vital to the demethylase activity, while JmjN domain complements JmjC enzymatic activity.[40] In physiology, the expression of KDM5B is restricted, being abundantly expressed in normal testes during spermatogenesis, and in murine embryonic mammary bud or mammary gland of pregnant mice.[39]

Molecular Functions of Lysine Demethylase 5B

Transcription elongation and alternative splicing

In humans, ~95% of multi-exon genes undergo alternative splicing. Alternative splicing of RNAs mediates and is essential for the translation of genomic information into functional proteins, regulation of gene expression, multiplicity of gene isoform, as well as protein diversity and complexity in higher eukaryotes.[41] Classically, transcription and alternative splicing are the two independent bio-processes, with the former almost always preceding the later; however, there is evidence of both occurring concomitantly, akin to histone demethylation.[42] In fact, the co-occurrence of co-transcriptional processes such as histone demethylation and splicing with the progression of RNA polymerase II (RNAPII) along the gene bodies facilitates transcription elongation and resets the underlying chromatin.[27]

Against the background of H3K4me3 enrichment at exon–intron junctions,[27,43] accruing evidence indicates that epigenetic modifications, or more specifically, histone demethylation, regulate transcription and splicing,[44,45] by recruiting splicing factors, chromatin structure compaction, with subsequent attenuation of polymerase II elongation rate and impaired transcription.[46] KDM5B plays an essential role in the regulation of RNAPII occupancy, transcriptional initiation, and elongation, as well as the process of alternative splicing in ES cells. He and Kidder in their seminal work demonstrated that KDM5B is enriched near alternatively spliced exons (exon skipping, cassette exons) and that short hairpin RNA-mediated depletion of KDM5B altered the occupancy of RNAPII promoter, resulting in attenuated RNAPII initiation and elongation rates in active and H3K4me3-marked genes in ES cells.[27]

Transcriptional regulation

Located upstream near the transcription start sites of genes, the 100–1000 base pair (bp) long promoter region of the DNA initiates transcription of genes. As already alluded, the silencing of KDM5B reduces H3K4me3 at promoter regions and at 5' exons nearby alternatively spliced exons, suggesting that KDM5B depletion may affect expression of exons near promoter regions.[27,43] The methylation of H3K4is linked with active transcription and combined with H3K27me3; the duo regulates the activities of genes that regulate development in a poised state.[30] Indeed, the transcription factor IID (TFIID), an integral subunit of the general transcription factors (TFs) that constitute the RNAPII preinitiation complex, has been suggested to bind to the H3K4me3 mark to induce/enhance its ability to facilitate the formation of the RNAPII preinitiation complex.[47] Once the TFIID binds to the TATA box within the promoter region of any gene of interest, the recruitment of other factors needed for RNAPII to start transcription is induced.

Moreover, the recognition of and interaction with H3K4me3 by chromatin-remodeling complexes open/uncoil the hitherto compacted 30-nm chromatin fiber (i.e., heterochromatin to euchromatin), facilitating transcription.[48] The regulation of gene expression in eukaryotes is premised on facilitating access of TFs to DNA sequences in the chromatin by chromatin-remodeling complexes, "which either chemically modify the core histones, mainly in their N-terminal tails, or use the energy of ATP hydrolysis to weaken the interaction of histones with DNA."[49] The nucleosome, which is the fundamental unit of chromatin, consists of paired H3, H4,

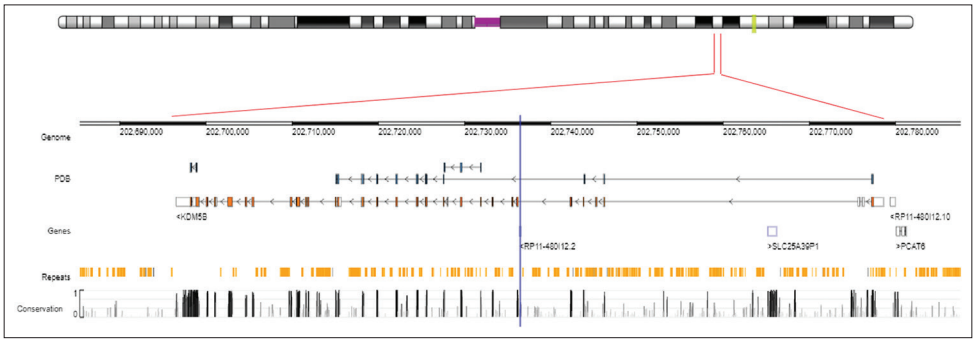

Figure 1: Schematic representation of lysine demethylase 5B genomic coordinates on the GRCh37/hg19 genome assembly. Lysine demethylase 5B is located in the 1q32.1 cytogenetic band of chromosome 1:202,696,526–202,778,598

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

H2A, and H2B core histones, acting as a spool, around which 147 bp of DNA is spun in 1.65 left-handed superhelix, with nucleosome–nucleosome repeats being facilitated by linker histone H1 and ~25 bps linker DNA. In essence, the histone H1 at the nucleosomal entry and exit sites restricts nucleosome mobility and facilitates chromatin folding and stability.[48,49] Recently, Vicent *et al*. demonstrated that within the 1st min of progesterone action, a complex collaborative influence of KDM5B, chromatin-remodeling complexes (nucleosome remodeling factor and activating signal cointegrator-2 complex), and the Cdk2/Cyclin A complex, on the chromatin fiber, mediates displacement of histone H1 and is requisite for gene induction and cell proliferation.[49] Their findings show that enhanced H3K4me3 signals sequel to localized displacement of KDM5B from the target chromatin elicits histone H1 displacement/depletion from target promoter regions, euchromatin reconfiguration and results in activation of transcription.

Posttranscriptional regulation

KDM5B does not only influence the regulation and development of transcription but is also associated with complex posttranscriptional regulations, such as maintenance of mRNA stability, mRNA translation, pre-mRNA splicing, and protein activities. Recently, it was demonstrated that the depletion of KDM5B impairs DNA repair, enhances DNA damage, induces p53 signaling, and sensitizes cells to genotoxic signals, highlighting its role as a vital "genome caretaker and a critical regulator of genomic stability."[50] In response to DNA damage, the protein level of the TF p53 oscillates, and its target genes exhibit a spectrum of time-dependent expression profile; this temporal expression dynamism in the target genes is dependent on target mRNA decay rate.[51] The manipulation of noncoding regions has been touted to influence mRNA stability, maintain polypeptide sequence, and keep protein identity; more recent evidence indicates altering the nucleotide sequences within the 3'-untranslated region (3'-UTR) of target mRNAs.[51-53] This is contextually significant as KDM5B with or without KDM5A recruits 3'-UTR processing machinery and promotes the alteration of the length of the 3'-UTR in target genes through its demethylase activity;[54] consistent with this, enhanced KDM5B expression and enzymatic activity have been shown to shorten the 3'-UTR of cyclin D1 and degrade cyclin D1 mRNA, while lengthening DICER1 3'-UTR in breast cancer cells.[54]

To prevent mRNA degradation and export, eukaryotic mRNAs are modified during transcription with a 5'-guanosine cap and a 3'-polyadenine (polyA) tail, which may be inserted at various sites after a stop codon without altering the coding sequence of the transcript product. While most mRNAs have a canonical polyA site, many harbor ≥1 alternative polyadenylation (APA) sites.[54-56] KDM5B through its H3K4me3 demethylase activity recruits polyadenylation machinery to the chromatin and processes and promotes alteration of the 3'-UTR in its target gene, and this is relevant considering that "cleavage of mRNA is tightly coupled with polyadenylation."[54] Through its interaction with transcripts and chromatin, KDM5B increases the pool of polyadenylation factors at proximal or distal polyA sites (including APA sites) and facilitates 3'-UTR processing at the sites. Consistent with KDM5B enrichment near promoter regions and at certain 3'-UTRs, there is enhanced recruitment of polyadenylation factors near promoter and terminator regions.[27,43,49,54] More practically, KDM5B has been shown to be essential for the recruitment of GATA3 to the *Foxa1* promoter for the induction of *Foxa1* expression, with concomitant increase in "the expression of key regulators of mammary morphogenesis and luminal lineage specification."[31] In addition, the enzymatic/demethylase activity of KDM5B was demonstrated to be indispensable for ES cell neural differentiation, especially as KDM5B "localizes predominantly at the transcription start sites of genes encoding developmental regulators."[30]

Physiological Functions of Lysine Demethylase 5B

Mammary gland development and function

Phenotypically, the loss of KDM5B function, as typified by KDM5B(−/−) mice models, elicited "decreased body weight, premature mortality, decreased female fertility, and delayed mammary gland development."[31] This phenotype was associated with reduced production of serum estrogen, diminished expression of principal regulators of mammary morphogenesis and luminal differentiation, such as FOXA1 and estrogen receptor (ER) α, impaired proliferation of mammary epithelial cells, fewer terminal end buds, lesser side branching, and defective ductal elongation in early puberty,[31,57] highlighting the critical regulatory role of KDM5B in breast development and function.

Neural development and function

In physiological conditions, high expression of KDM5B is noted during embryogenesis, in ES cells, and in adult testis, brain, spleen, and thymus.[30] Further, under the purview of KDM5B is neural differentiation and neurogenesis. It has been shown that almost all target genes of KDM5B are H3K4me3-associated, and the depletion of KDM5B in ES cells impedes their differentiation toward the neural lineage.[30] Against this background, and consistent with contemporary knowledge that gene silencing or suppressed activity is associated with loss of H3K4me2/3, gain of DNAme, or *de novo* H3K27 me,[58,59] it is comprehensible that impaired differentiation is invariably due to failed silencing of earlier activated genes, including pluripotency and germ cell-related genes, and not because of probable "failed activation of lineage-specific genes or erroneous induction of alternative lineage genes."[30,58,59] Thus, the inactivation of KDM5B elicits global increases in promoter H3K4me3 levels of target genes, with impaired silencing of stemness and germ cell genes. This is further validated by the findings from Zhou *et al*. demonstrating that shRNA-mediated depletion of KDM5B attenuated the proliferation rate in proliferating adult neural

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

stem cells and reduced their ability to form neurospheres, as well as enhanced H3K4me3 at the proximal promoter region of reelin (Reln) in differentiating adult neural stem cells.[27] These studies indicate that KDM5B negatively regulates neurogenesis and function.

Pancreatic endocrine maturation, glucose homeostasis, and islet function

Recently, the probable role of KDM5B in the regulation of pancreatic development, maintenance of homeostasis in glucose metabolism, and function of the islet of Langerhans began to emerge. This was first posited based on the results of a causal reasoning approach, indicating that KDM5B in concert with neurogenin-3 (NEUROG3) and E2F TF 1 (E2F1) is actively involved in the endocrine cell development.[60] Against the background that NEUROG3 drives pancreatic β cell development and function,[61] and that E2F1 that stimulates β cell proliferation and function binds directly to and activates NEUROG3 in the embryonic pancreas,[62,63] it was demonstrated that KDM5B negatively regulates E2F1 and NEUROG3, with concomitant suppression of H3K4me3, and results in impaired endocrine β cell production, proliferation, maturation, and function.[60] These findings were further corroborated by Backe *et al*.[64] in their work, demonstrating that on depletion of KDM5B (KDM5B-KO) in NOD/SCID mice, the KDM5B-knockout (KO) mice exhibited retarded growth, reduced body weight, and reduced serum insulin (Ins) levels, despite normoglycemia, suggesting high Ins sensitivity – a condition wherein blood sugar is reduced by enhanced utilization of blood glucose by the body cells. This is consistent with evolving knowledge that increased H3K4me3 levels sequel to depletion of KDM5B is important for transcription of β cell genes, including Ins 1, Ins 2, and glucose transporter 2 (Glut2). This is suggestive of the β cells-protective and function-enhancing roles of H3K4 methylation by KDM5B inhibition.[65]

Skeletal myogenesis and osteogenesis

There is also evidence of a regulatory role for KDM5B in skeletal myogenesis. It was recently reported that the transcriptional activation or repression of the RUNX family TF 2 (Runx2) gene through modulation of the osteoblast-specific Runx2-P1 promoter (which encodes for Runx2/p57 mRNA isoform) is associated with the selective "writing" or "erasing" of histone marks, including H3K4me2/3, during the osteogenic and myoblastic differentiation of the mesenchymal cells.[32] Contextually, silencing KDM5B enhances H3K4me2/3 marks at the bone-specific Runx2-P1 promoter region and elicits ectopic expression of Runx2/p57 and osteocalcin, which in turn activates or impedes the suppression of the Runx2-P1 promoter during the differentiation of mesenchymal cells to myogenic lineage;[32] thus, indicating that KDM5B is a major epigenetic switch that determines the myogenic and/or osteogenic fate of mesenchymal cells. Consistent with the above, it has also been demonstrated that KDM5B, an "eraser" of H3K4me2/3, epigenetically controls the mesenchymal stem cells (MSCs) osteoblastic potential by repressing expression of the bone master-gene Runx2 in MS cells derived from the human umbilical cord Wharton's jelly mesenchymal stem cells (WJ-MSCs); more specifically, it was shown that KDM5B loss-of-function enhanced the expression of RUNX2/p57 in the WJ-MSCs during commitment to osteogenic differentiation.[66]

Prenatal development, gametogenesis, and fertility

Summarily, prenatal development is strictly controlled by TFs and chromatin-associated proteins, with H3K4me3, H3K27me3, or H3K4me3/H3K27me3 combination being associated with active transcription, gene repression, or poised state, respectively. It is posited that this constitutive potential of histone modifications to modulate transcriptional state may be associated with the capacity to influence or determine cellular identity, cell fate, and development.[11,12,30] This rationalization was validated by recent findings demonstrating that enhanced deposition of H3K4me3 during embryonic development upregulated the expression of neural master regulators such as Otx2 and Pax6 in KDM5B-KO brains while the depletion of KDM5B (an "eraser" of H3K4me2/3 marks) caused severe respiratory failure; This resulted in severe neonatal lethality, such as dysfunctional cranial nerves, defective eye development, high incidence of exencephaly, and homeotic skeletal transformation in the KDM5B−/− embryos.[67]

In addition, KDM5B is a demonstrated marker for early spermatogonia, as the inactivation of KDM5B is requisite for the differentiation of spermatogonia into spermatocytes,[68] and a decrease in the number of mature spermatozoa/sperms is associated with an increase in KDM5B mRNA level.[69] We believe that a mechanistic understanding of this is translationally relevant for fertility as it is probable that KDM5B interacts with poly (ADP-ribose) polymerase 1 (PARP1) during spermatogenesis, as is suggested by the binding of PARP1 to active promoter regions associated with KDM5B occupancy in the somatic cells.[70] We posit that in gametes or germ cells, this "co-occupancy" may mean that PARP1 ADP-ribosylates KDM5B and impair the capability of KDM5B to "erase" H3K4me3, thus maintaining the active H3K4me3 pool and keeping spermatogenesis genes active. Moreover, during meiosis, constitutive formation of DNA double-strand breaks (DSBs) triggers homologous recombination DSB repair machinery; considering that enhanced PARP1 activity has been demonstrated in the vicinity of DNA damage/strand break,[71] it is conceivable that akin to KDM5A, KDM5B may be recruited by PARP1 to the DSB sites to facilitate H3K4me3 deletion, silence DSB effector genes, and induce homologous recombination DSB repair machinery, which is crucial in elongating spermatids.[72] In light of these findings, and the high expression of KDM5B in the testis (spermatogonia stem cells >> sertoli or leydig cells) compared to other tissues,[68,73] it is thus safe to say that KDM5B plays an essential role in male fertility.

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

Pathological Roles of Lysine Demethylase 5B

Lysine demethylase 5B and cancer

Besides its physiological relevance, the undulating landscape of histone modification is implicated in various diseases, including cancer.[74] Aberrant expression of KDM5B has been associated with triple-negative, luminal (ER+, PR+, HER2±, Ki-67^{high}), ER-positive, or invasive ductal breast cancer.[36,37,57,75-78] Similarly, high KDM5B expression has been documented in the skin and uveal melanomas[79,80] and is essential for continuous growth of a subpopulation of multidrug-resistant slow-cycling melanoma cells.[81,82] This oncogenic role of KDM5B has also been documented in non-small cell lung carcinoma,[33] hepatocellular carcinoma,[83] poor prognosis head-and-neck squamous cell carcinoma,[84] radio-resistant oral squamous cell carcinoma,[85] esophageal carcinoma,[86] bladder cancer,[87] gastric cancer,[88] chemoresistant ovarian cancer,[89] and neuroblastoma.[35] In these cases, the negative modulation of KDM5B significantly inhibits cancerous cell proliferation and motility (migration, invasion), suppresses clonogenicity and cancer stem cell-like phenotype, impedes metastasis, resensitizes to therapy, and/or elicits good prognosis, thus projecting KDM5B as an actionable molecular or pharmacological target for anticancer therapy.

Lysine demethylase 5B, tissue fibrosis, and aging

The availability of oxygen or the lack thereof plays a crucial role in human energy metabolism, considering that ischemia or associated hypoxia impairs tissue homeostasis. Hypoxia, a feature of chronic age-related diseases in the presence of impaired tissue perfusion, stabilizes the expression of the master transcriptional regulator of cellular and developmental response to hypoxia, hypoxia-inducible TF (HIF)-1α.[90] HIF-1α induces the expression of several KDMs including KDM5B which "erases" H3K4me2/3 activating marks; chronic induction of the HIF-1α/KDM5B signaling with resultant transcriptional inhibition of E2F-dependent cell cycle genes triggers the formation of senescence-associated heterochromatic foci and elicits cellular senescence and tissue fibrosis, and this state of perpetual inhibition of cell replication/proliferation and progressive deposition of collagen fibers is positively correlated with aging and most age-related pathology.[90-92]

The H3K4me3 mark has been associated with longevity, and depending on environmental context or specific enzyme, the depletion of H3K4me3 enzymes either lengthens or shortens lifespan. For example, while silencing of the H3K4 methyltransferases, SET domain-containing 1A (SETD1A) and SETD2 increased the lifespan of *Caenorhabditis elegans*, the maintaining of H3K4me3 mark via the silencing of KDM5B shortened the lifespan of C. elegans hermaphrodites and male *Drosophila*.[93,94] Together, the data pool does suggest that KDM5B-induced loss of H3K4me3 is beneficial to longevity.[95]

Lysine demethylase 5B in neurodevelopmental disorders, neurodegeneration, and intellectual disability

Consistent with the role of KDM5B in the neural development and function alluded above,[27,30,58,59] it would not be out of place that mutations, whether loss-of-gain or gain-of-function alterations in KDM5B gene, could disrupt neuronal differentiation and result in cognitive deficiencies. The last two decades has been characterized by increasing documentation of the role of histone modification, and more particularly, KDM5B-regulated H3K4me3 alteration in recessive cognitive disorders, including several intellectual disability (ID) syndromes[96-98] and autism spectrum disorder (ASD).[99] Utilizing next-generation sequencing, it has now been demonstrated a *de novo* splicing mutation (c.283A>G) in KDM5B in a case of nonsyndromic ID,[98] with six other new variants in a large cohort of patients with ASD using whole exome sequencing.[99,100] Moreover, alongside "erasers" of H3K4me1/2/3, KDM1A/LSD1, KDM5A, and KDM5C, mutation (s) in KDM5B has been implicated in neurodevelopmental disorders; documented alterations in KDM5B include missense mutation in the JmjN and zinc finger domains, nonsense mutation in the PHD and PLU-1 domains, frameshift in the PHD domain, and splicing mutation in regions between the JmjN and ARID domain,[101] and more recently, chromosome microarray and quantitative PCR analyses revealed that patients with ID, coordination disorder, retarded growth, and several dysmorphic features harbor microduplications involving 1q32.1.[102]

A schematic depiction of these pleiotropic roles of KDM5B in both physiology and pathology is shown in Figure 2.

Therapeutic Potential of Targeting Lysine Demethylase 5B

Accruing evidence ascribes a crucial role to KDM5B in the regulation of many biological processes –physiological and pathological, embryonic development, organogenesis, neurologic disorders, cardiovascular diseases, and malignancies. It is thus not without evidential basis that the therapeutic targeting KDM5B and/or manipulation of its expression would constitute an efficacious treatment strategy in the context of systemic diseases.

Maintenance of endothelial health and cardiovascular homeostasis

Consistent with contemporary knowledge, maintaining or reinstating endothelial physiology prevents or represses atherosclerosis, boosts vasodilatation, facilitates "normal" anticoagulation, and elicits angiogenesis; however, endothelial injury or dysfunction erodes these properties and as such reprograms endothelial cells to promote development of vascular diseases.[103,104] The alteration of epigenetic marks, including modification of H3K4me3, is touted as an innovative strategy to modulate the switching of endothelial phenotype and disrupt the initiation and/or progression of vascular diseases.[103] Recently, the shRNA-mediated targeting of KDM5B in the human umbilical vein endothelial cells (HUVECs) was shown to attenuate endothelial cell migration, vessel sprouting, and tube formation, just as the pharmacological inhibition of KDM5B or ectopic expression

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

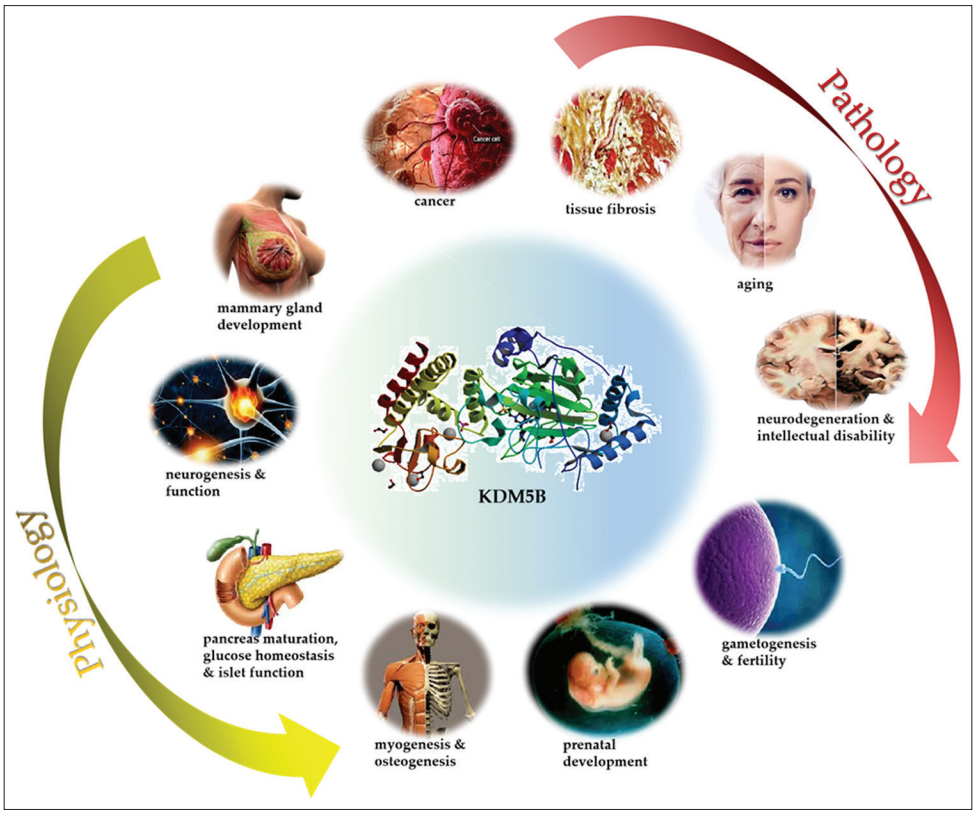

Figure 2: Schematic depiction of the pleiotropic roles of lysine demethylase 5B in physiology and pathology

of a catalytic-inactive KDM5B mutant suppressed HUVEC angiogenicity.[105] Together, these findings highlight the relevance of KDM5B in vascular biology, indicate its role as a vital regulator of endothelial angiogenic potential, and demonstrate that the therapeutic manipulation of KDM5B catalytic activity can help maintain endothelial health and cardiovascular homeostasis.

Immunotherapy and boosting innate immune response

The ability of pathogens to evade immunosurveillance is intrinsic to their pathogenicity and virulence; thus, the maintenance or restoration of an unimpaired immunosurveillance is an efficacious prophylaxis and treatment strategy. The stimulator of interferon genes (STING) plays a vital role in the constitutive pathogen-targeting immune response of hosts. KDM5B binds to the STING locus, and the catalytic activity of KDM5B suppresses the capability of STING to elicit innate and/or adaptive immune responses.[106] There is evidence that suppressing or inhibiting KDM5B elicits reactivation of the STING signaling, increases the expression of interferon stimulating genes, induces profound interferon response, enhances immune cell pooling, impedes viral infection, and results in better clinical outcome.[106,107] These findings that the inhibition of KDM5B provide prompt, robust, and reversible modulation of innate immune response has significant clinical implications for the management of immune-related pathology, including infections and cancer. In fact, some KDM5 inhibitors are already in clinical trials for treatment of hepatitis B infection.[106,108] Together, these findings suggest that small molecule inhibitors of KDM5B may serve as adjuvant for other immunotherapies and that further exploration of the molecular underlining and pharmacology of KDM5B inhibitors could lead to the development of a new class of immunotherapeutic drugs.

Managing metabolic disorders and normalization of metabolism

KDM5B has been shown to activate genes that regulate mitochondrial function and metabolism. Investigation of genes regulated by KDM5 revealed the enrichment for diverse biological processes, including cell division, glycosylation, protein synthesis, glucose metabolism, and lipid metabolism, with concomitant implication of the deferentially-expressed genes in the functioning of several subcellular compartments, such as the mitochondria, ribosomes, and lipid particles.[109] In fact, KDM5-mutant flies were shown to have dysmorphic mitochondria in addition to metabolic deficiency, resulting in reduced ATP production, impaired lipid metabolism, and enhanced oxidative stress.[109] In concert with the above, documented positive correlation between upregulated KDM5B expression and increased mitochondrial bioenergy[82,109] informs the inference that the therapeutic exploitation of KDM5B may present a novel clinically-feasible approach for the reversal of mitochondrial dysfunction and normalization of metabolism.[109-111]

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

Curtailing neurodegeneration and enhancing cognitive function

As alluded already, KDM5B expression and/or activity determine cell fate and drive the differentiation of ESCs to neuronal lineage,[27,30,58,59,101] while KDM5B-regulated H3K4me3 alteration is implicated in recessive cognitive disorders, including several ID syndromes[96-98] and ASD.[99] Consistent with the role of KDM5B in neurogenesis and survival, neuronal plasticity, and regeneration, it is probable that KDM5B mimetics can ameliorate disease by oscillatory prevention of neuronal death and enhanced neural repair. Cognizant with the functional crosstalk between KDMs and histone deacetylases (HDACs) in chromatin remodeling and regulation of gene transcription, as well as evidence indicating that inhibitors targeting the zinc co-factor-dependent HDAC classes I and II, but not NAD(+)-dependent HDAC class III, elicit significant upregulation of H3K4me2[112] which is a substrate of KDM5B, we posit from a therapeutic perspective that converses to HDAC inhibitors, the pharmacological inhibition of H3K4me2/3 by KDM5B agonists or mimetics, mediated in part by "increased H3K27 me3 and decreased H3K9ac,"[113] with concomitant downregulation of peroxiredoxins, H_2O_2 detoxification, and suppression of oxidative stress,[114] may elicit similar broad therapeutic efficacy in several neurodevelopmental or neurodegenerative disorders, including Coffin-Lowry syndrome, spinal muscular atrophy, Friedreich's ataxia, Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.[115] Together, these features make the case for the exploration of KDM5B mimetic/agonist therapy as prospective neuroprophylaxis and/or neurotherapeutics.

Lysine demethylase 5B: An actionable anticancer molecular target

KDM5B is increasingly being touted as an H3K4me2/3-demethylating oncogene. H3K4me2/3 residues constitute the transcription initiation sites of active transcription genes, while H3K4me2/3 demethylation elicits transcriptional repression of tumor suppressors, in most cases. The ability of KDM5B to erase H3K4me2/3 activation marks is of therapeutic relevance, just as much as its capability to regulate chromatin structure by modulating several repressive transcriptional complexes in the vicinity of the promoter regions of its target genes. The discovery and validation of biomarkers such as KDM5B are requisite for improving patient monitoring, prediction of therapy response, and clinical prognostication. The reversibility of epigenetic players such as KDM5B offers an exploitable opportunity to impede pathobiological processes and ameliorate disease symptoms through epigenetic-based therapy (i.e., so-called epidrugs). As an evolving field, clinical epigenetics transcends simply demystifying the biology of diseases; its clinical feasibility is currently being explored in the management of patients with cancer, infectious diseases, and neurological and immunological disorders.[116] Indeed, as earlier alluded in this review, our team and many others have provided *in silico*, *in vitro*, *in vivo*, and/or *ex vivo* evidence that the molecular or pharmacological targeting of KDM5B inhibits "aggressive," "cancer stem cell-like," "chemoresistant," "radioresistant," "metastatic," "multidrug-resistant" carcinomas of various histological origins.[33,35-37,74-89] However, the integration of epigenetic preclinical data to derive reliable biomarkers that are measureable, time-efficient, and cost-effective in routine clinical practice remains a challenge.

It is contextually relevant that Sayegh *et al*., using an AlphaScreen technology-based high-throughput screen of 15,134 small molecules, identified some "drug-like" nonspecific inhibitors of KDM5B, including 2,4-pyridinedicarboxylic acid (2,4-PDCA) (IC_{50}: ~5 μm), catechols, namely caffeic acid (mean IC_{50}: ~2.3 μm) and esculetin (mean IC_{50}: ~3.6 μm), and more importantly, 2-4 (4-methylphenyl)-1,2-benzisothiazol-3 (2H)-one (PBIT), which inhibits about 95% of KDM5B *in vitro* (IC_{50}: ~3 μm); however, their inhibitory effect is nonspecific to KDM5B.[117] The identification of these nonspecific KDM5B inhibitors highlights the potential of developing such "drug-like" molecules for clinical use either as a single agent or in combination with other drugs. In fact, the therapeutic targetability of KDM5B in cancer has been succinctly addressed,[118] and as rightly put by Zheng *et al*., "KDM5B is considered as a promising drug target for cancer therapy, and many medicinal chemists are trying to design and synthesize potent and selective KDM5B inhibitors with the aid of high-throughput screening (HTS), structure-based drug design, and structure activity relationship (SAR) studies.[118]"

In light of all these, variance in KDM5B expression not only allows for early diagnosis of cancer and accurate prognostication, but it also carries the promise for being an efficacious anticancer strategy and thus provides a clinical rationale for the design and synthesis of potent and highly selective KDM5B inhibitors using HTS, rational (structure-based and/or function-based) drug design, and SAR studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Dupont C, Armant DR, Brenner CA. Epigenetics: Definition, mechanisms and clinical perspective. Semin Reprod Med 2009;27:351-7.
2. Nagy C, Turecki G. Transgenerational epigenetic inheritance: An open discussion. Epigenomics 2015;7:781-90.
3. Nicoglou A, Merlin F. Epigenetics: A way to bridge the gap between biological fields. Stud Hist Philos Biol Biomed Sci 2017;66:73-82.
4. Felsenfeld G. A brief history of epigenetics. Cold Spring Harb Perspect Biol 2014;6. pii: A018200.
5. Felsenfeld G. The evolution of epigenetics. Perspect Biol Med 2014;57:132-48.
6. Fan J, Krautkramer KA, Feldman JL, Denu JM. Metabolic regulation of histone post-translational modifications. ACS Chem Biol

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

2015;10:95-108.
7. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res 2011;21:381-95.
8. Lawrence M, Daujat S, Schneider R. Lateral thinking: How histone modifications regulate gene expression. Trends Genet 2016;32:42-56.
9. Stewart MD, Li J, Wong J. Relationship between histone H3 lysine 9 methylation, transcription repression, and heterochromatin protein 1 recruitment. Mol Cell Biol 2005;25:2525-38.
10. Chen F, Kan H, Castranova V. Methylation of lysine 9 of histone H3: Role of heterochromatin modulation and tumorigenesis. In: Tollefsbol T, editor. Handbook of Epigenetics: The New Molecular and Medical Genetics. Ch. 10. Cambridge, MA: Academic Press. Elsevier Inc.; 2011. p. 149-57.
11. Kimura H. Histone modifications for human epigenome analysis. J Hum Genet 2013;58:439-45.
12. Howe FS, Fischl H, Murray SC, Mellor J. Is H3K4me3 instructive for transcription activation? Bioessays 2017;39:1-2.
13. Hyun K, Jeon J, Park K, Kim J. Writing, erasing and reading histone lysine methylations. Exp Mol Med 2017;49:e324.
14. Dimitrova E, Turberfield AH, Klose RJ. Histone demethylases in chromatin biology and beyond. EMBO Rep 2015;16:1620-39.
15. Black JC, Van Rechem C, Whetstine JR. Histone lysine methylation dynamics: Establishment, regulation, and biological impact. Mol Cell 2012;48:491-507.
16. Kooistra SM, Helin K. Molecular mechanisms and potential functions of histone demethylases. Nat Rev Mol Cell Biol 2012;13:297-311.
17. Johansson C, Tumber A, Che K, Cain P, Nowak R, Gileadi C, *et al*. The roles of Jumonji-type oxygenases in human disease. Epigenomics 2014;6:89-120.
18. Faundes V, Newman WG, Bernardini L, Canham N, Clayton-Smith J, Dallapiccola B, *et al*. Histone lysine methylases and demethylases in the landscape of human developmental disorders. Am J Hum Genet 2018;102:175-87.
19. Maes T, Mascaró C, Ortega A, Lunardi S, Ciceri F, Somervaille TC, *et al*. KDM1 histone lysine demethylases as targets for treatments of oncological and neurodegenerative disease. Epigenomics 2015;7:609-26.
20. Harmeyer KM, Facompre ND, Herlyn M, Basu D. JARID1 histone demethylases: Emerging targets in cancer. Trends Cancer 2017;3:713-25.
21. Park SY, Park JW, Chun YS. Jumonji histone demethylases as emerging therapeutic targets. Pharmacol Res 2016;105:146-51.
22. Jambhekar A, Anastas JN, Shi Y. Histone lysine demethylase inhibitors. Cold Spring Harb Perspect Med 2017;7. pii: a026484.
23. 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.
24. Zhang Y, Yang H, Guo X, Rong N, Song Y, Xu Y, *et al*. The PHD1 finger of KDM5B recognizes unmodified H3K4 during the demethylation of histone H3K4me2/3 by KDM5B. Protein Cell 2014;5:837-50.
25. Klein BJ, Piao L, Xi Y, Rincon-Arano H, Rothbart SB, Peng D, *et al*. The histone-H3K4-specific demethylase KDM5B binds to its substrate and product through distinct PHD fingers. Cell Rep 2014;6:325-35.
26. Horton JR, Engstrom A, Zoeller EL, Liu X, Shanks JR, Zhang X, *et al*. Characterization of a linked jumonji domain of the KDM5/JARID1 family of histone H3 lysine 4 demethylases. J Biol Chem 2016;291:2631-46.
27. He R, Kidder BL. H3K4 demethylase KDM5B regulates global dynamics of transcription elongation and alternative splicing in embryonic stem cells. Nucleic Acids Res 2017;45:6427-41.
28. Xie L, Pelz C, Wang W, Bashar A, Varlamova O, Shadle S, *et al*. KDM5B regulates embryonic stem cell self-renewal and represses cryptic intragenic transcription. EMBO J 2011;30:1473-84.
29. Zhou Q, Obana EA, Radomski KL, Sukumar G, Wynder C, Dalgard CL, *et al*. Inhibition of the histone demethylase Kdm5b promotes neurogenesis and derepresses Reln (reelin) in neural stem cells from the adult subventricular zone of mice. Mol Biol Cell 2016;27:627-39.
30. Schmitz SU, Albert M, Malatesta M, Morey L, Johansen JV, Bak M, *et al*. Jarid1b targets genes regulating development and is involved in neural differentiation. EMBO J 2011;30:4586-600.
31. Zou MR, Cao J, Liu Z, Huh SJ, Polyak K, Yan Q. Histone demethylase jumonji At-rich interactive domain 1B (JARID1B) controls mammary gland development by regulating key developmental and lineage specification genes. J Biol Chem 2014;289:17620-33.
32. Rojas A, Aguilar R, Henriquez B, Lian JB, Stein JL, Stein GS, *et al*. Epigenetic control of the bone-master runx2 gene during osteoblast-lineage commitment by the histone demethylase JARID1B/KDM5B. J Biol Chem 2015;290:28329-42.
33. Kuo KT, Huang WC, Bamodu OA, Lee WH, Wang CH, Hsiao M, *et al*. Histone demethylase JARID1B/KDM5B promotes aggressiveness of non-small cell lung cancer and serves as a good prognostic predictor. Clin Epigenetics 2018;10:107.
34. Zhang J, An X, Han Y, Ma R, Yang K, Zhang L, *et al*. Overexpression of JARID1B promotes differentiation via SHIP1/AKT signaling in human hypopharyngeal squamous cell carcinoma. Cell Death Dis 2016;7:e2358.
35. Kuo YT, Liu YL, Adebayo BO, Shih PH, Lee WH, Wang LS, *et al*. JARID1B expression plays a critical role in chemoresistance and stem cell-like phenotype of neuroblastoma cells. PLoS One 2015;10:e0125343.
36. Bamodu OA, Huang WC, Lee WH, Wu A, Wang LS, Hsiao M, *et al*. Aberrant KDM5B expression promotes aggressive breast cancer through MALAT1 overexpression and downregulation of hsa-miR-448. BMC Cancer 2016;16:160.
37. Yamamoto S, Wu Z, Russnes HG, Takagi S, Peluffo G, Vaske C, *et al*. JARID1B is a luminal lineage-driving oncogene in breast cancer. Cancer Cell 2014;25:762-77.
38. Dorosz J, Kristensen LH, Aduri NG, Mirza O, Lousen R, Bucciarelli S, *et al*. Molecular architecture of the Jumonji C family histone demethylase KDM5B. Sci Rep 2019;9:4019.
39. Scibetta AG, Santangelo S, Coleman J, Hall D, Chaplin T, Copier J, *et al*. Functional analysis of the transcription repressor PLU-1/JARID1B. Mol Cell Biol 2007;27:7220-35.
40. Klose RJ, Kallin EM, Zhang Y. JmjC-domain-containing proteins and histone demethylation. Nat Rev Genet 2006;7:715-27.
41. Thakur PK, Rawal HC, Obuca M, Kaushik S. Bioinformatics approaches for studying alternative splicing.' In: Ranganathan S, Gribskov M, Nakai K, Schönbach C, editors. Reference Module in Life Sciences. Encyclopedia of Bioinformatics and Computational Biology: ABC of Bioinformatics. Vol. 2. Amsterdam, The Netherlands: Elsevier Inc.; 2019. p. 221-34.
42. Kornblihtt AR, Schor IE, Alló M, Dujardin G, Petrillo E, Muñoz MJ. Alternative splicing: a pivotal step between eukaryotic transcription and translation. Nat Rev Mol Cell Biol 2013;14:153-65.
43. Zhou Y, Lu Y, Tian W. Epigenetic features are significantly associated with alternative splicing. BMC Genomics 2012;13:123.
44. Khan DH, Jahan S, Davie JR. Pre-mRNA splicing: Role of epigenetics and implications in disease. Adv Biol Regul 2012;52:377-88.
45. Luco RF, Allo M, Schor IE, Kornblihtt AR, Misteli T. Epigenetics in alternative pre-mRNA splicing. Cell 2011;144:16-26.
46. Pacini C, Koziol MJ. Bioinformatics challenges and perspectives when studying the effect of epigenetic modifications on alternative splicing. Philos Trans R Soc Lond B Biol Sci 2018;373. pii: 20170073.
47. Vermeulen M, Mulder KW, Denissov S, Pijnappel WW, van Schaik FM, Varier RA, *et al*. Selective anchoring of TFIID to nucleosomes by trimethylation of histone H3 lysine 4. Cell 2007;131:58-69.
48. Clapier CR, Cairns BR. The biology of chromatin remodeling complexes. Annu Rev Biochem 2009;78:273-304.
49. Vicent GP, Nacht AS, Font-Mateu J, Castellano G, Gaveglia L, Ballaré C, *et al*. Four enzymes cooperate to displace histone H1 during the first minute of hormonal gene activation. Genes Dev 2011;25:845-62.
50. Li X, Liu L, Yang S, Song N, Zhou X, Gao J, *et al*. KDM5B regulates genome stability. Proc Nat Acad Sci 2014;111:7096-101.
51. Koh WS, Porter JR, Batchelor E. Tuning of mRNA stability through altering 3'-UTR sequences generates distinct output expression in a synthetic circuit driven by p53 oscillations. Sci Rep 2019;9:5976.
52. Grzybowska EA, Wilczynska A, Siedlecki JA. Regulatory functions of 3'UTRs. Biochem Biophys Res Commun 2001;288:291-5.

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

53. Mayr C. Regulation by 3'-Untranslated Regions. Annu Rev Genet 2017;51:171-94.
54. Blair LP, Liu Z, Labitigan RL, Wu L, Zheng D, Xia Z, *et al*. KDM5 lysine demethylases are involved in maintenance of 3'UTR length. Sci Adv 2016;2:e1501662.
55. Shi Y. Alternative polyadenylation: New insights from global analyses. RNA 2012;18:2105-17.
56. Mata J. Genome-wide mapping of polyadenylation sites in fission yeast reveals widespread alternative polyadenylation. RNA Biol 2013;10:1407-14.
57. Catchpole S, Spencer-Dene B, Hall D, Santangelo S, Rosewell I, Guenatri M, *et al*. PLU-1/JARID1B/KDM5B is required for embryonic survival and contributes to cell proliferation in the mammary gland and in ER+breast cancer cells. Int J Oncol 2011;38:1267-77.
58. Mohn F, Weber M, Rebhan M, Roloff TC, Richter J, Stadler MB, *et al*. Lineage-specific polycomb targets and de novo DNA methylation define restriction and potential of neuronal progenitors. Mol Cell 2008;30:755-66.
59. Meissner A, Mikkelsen TS, Gu H, Wernig M, Hanna J, Sivachenko A, *et al*. Genome-scale DNA methylation maps of pluripotent and differentiated cells. Nature 2008;454:766-70.
60. Gutteridge A, Rukstalis JM, Ziemek D, Tié M, Ji L, Ramos-Zayas R, *et al*. Novel pancreatic endocrine maturation pathways identified by genomic profiling and causal reasoning. PLoS One 2013;8:e56024.
61. Gradwohl G, Dierich A, LeMeur M, Guillemot F. neurogenin3 is required for the development of the four endocrine cell lineages of the pancreas. Proc Natl Acad Sci U S A 2000;97:1607-11.
62. Grouwels G, Cai Y, Hoebeke I, Leuckx G, Heremans Y, Ziebold U, *et al*. Ectopic expression of E2F1 stimulates beta-cell proliferation and function. Diabetes 2010;59:1435-44.
63. Kim SY, Rane SG. The Cdk4-E2f1 pathway regulates early pancreas development by targeting Pdx1+ progenitors and Ngn3+ endocrine precursors. Development 2011;138:1903-12.
64. Backe MB, Jin C, Andreone L, Sankar A, Agger K, Helin K, *et al*. The Lysine Demethylase KDM5B Regulates Islet Function and Glucose Homeostasis. J Diabetes Res 2019;2019:5451038.
65. Backe MB, Andersson JL, Bacos K, Christensen DP, Hansen JB, Dorosz JJ, *et al*. Lysine demethylase inhibition protects pancreatic ß cells from apoptosis and improves ß-cell function. Mol Cell Endocrinol 2018;460:47-56.
66. Bustos F, Sepúlveda H, Prieto CP, Carrasco M, Díaz L, Palma J, *et al*. Runt-related transcription factor 2 induction during differentiation of Wharton's Jelly Mesenchymal stem cells to osteoblasts is regulated by Jumonji AT-rich interactive domain 1b histone demethylase. Stem Cells 2017;35:2430-41.
67. Albert M, Schmitz SU, Kooistra SM, Malatesta M, Morales Torres C, Rekling JC, *et al*. The histone demethylase Jarid1b ensures faithful mouse development by protecting developmental genes from aberrant H3K4me3. PLoS Genet 2013;9:e1003461.
68. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nat Rev Cancer 2005;5:615-25.
69. Usik MA, Ogneva IV. Cytoskeleton Structure in Mouse Sperm and Testes After 30 Days of Hindlimb Unloading and 12 Hours of Recovery. Cell Physiol Biochem 2018;51:375-92.
70. Krishnakumar R, Kraus WL. PARP-1 regulates chromatin structure and transcription through a KDM5B-dependent pathway. Mol Cell 2010;39:736-49.
71. Goldberg M. KDM4D crosstalks with PARP1 and RNA at DNA DSBs. Cell Cycle 2015;14:1495.
72. 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;216:1959-74.
73. Cui Y, Zhang Y, Wei Z, Gao J, Yu T, Chen R, *et al*. Pig KDM5B: MRNA expression profiles of different tissues and testicular cells and association analyses with testicular morphology traits. Gene 2018;650:27-33.
74. Chi P, Allis CD, Wang GG. Covalent histone modifications – Miswritten, misinterpreted and mis-erased in human cancers. Nat Rev Cancer 2010;10:457-69.
75. Lu PJ, Sundquist K, Baeckstrom D, Poulsom R, Hanby A, Meier-Ewert S, *et al*. A novel gene (PLU-1) containing highly conserved putative DNA/chromatin binding motifs is specifically up-regulated in breast cancer. J Biol Chem 1999;274:15633-45.
76. Yamane K, Tateishi K, Klose RJ, Fang J, Fabrizio LA, Erdjument-Bromage H, *et al*. PLU-1 is an H3K4 demethylase involved in transcriptional repression and breast cancer cell proliferation. Mol Cell 2007;25:801-12.
77. 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;286:40531-5.
78. Zhao LH, Liu HG. Immunohistochemical detection and clinicopathological significance of JARID1B/KDM5B and P16 expression in invasive ductal carcinoma of the breast. Genet Mol Res 2015;14:5417-26.
79. Kuźbicki L, Lange D, Strączyńska-Niemiec A, Chwirot BW. JARID1B expression in human melanoma and benign melanocytic skin lesions. Melanoma Res 2013;23:8-12.
80. Radberger P, Radberger A, Bykov VJ, Seregard S, Economou MA. JARID1B protein expression and prognostic implications in uveal melanoma. Invest Ophthalmol Vis Sci 2012;53:4442-9.
81. Roesch A, Fukunaga-Kalabis M, Schmidt EC, Zabierowski SE, Brafford PA, Vultur A, *et al*. A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. Cell 2010;141:583-94.
82. Roesch A, Vultur A, Bogeski I, Wang H, Zimmermann KM, Speicher D, *et al*. Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling JARID1B (high) cells. Cancer Cell 2013;23:811-25.
83. Wang D, Han S, Peng R, Jiao C, Wang X, Yang X, *et al*. Depletion of histone demethylase KDM5B inhibits cell proliferation of hepatocellular carcinoma by regulation of cell cycle checkpoint proteins p15 and p27. J Exp Clin Cancer Res 2016;35:37.
84. Huang D, Qiu Y, Li G, Liu C, She L, Zhang D, *et al*. KDM5B overexpression predicts a poor prognosis in patients with squamous cell carcinoma of the head and neck. J Cancer 2018;9:198-204.
85. Lin CS, Lin YC, Adebayo BO, Wu A, Chen JH, Peng YJ, *et al*. Silencing JARID1B suppresses oncogenicity, stemness and increases radiation sensitivity in human oral carcinoma. Cancer Lett 2015;368:36-45.
86. Kano Y, Konno M, Ohta K, Haraguchi N, Nishikawa S, Kagawa Y, *et al*. Jumonji/Arid1b (Jarid1b) protein modulates human esophageal cancer cell growth. Mol Clin Oncol 2013;1:753-7.
87. Li X, Su Y, Pan J, Zhou Z, Song B, Xiong E, *et al*. Connexin 26 is down-regulated by KDM5B in the progression of bladder cancer. Int J Mol Sci 2013;14:7866-79.
88. Wang Z, Tang F, Qi G, Yuan S, Zhang G, Tang B, *et al*. KDM5B is overexpressed in gastric cancer and is required for gastric cancer cell proliferation and metastasis. Am J Cancer Res 2015;5:87-100.
89. Wang L, Mao Y, Du G, He C, Han S. Overexpression of JARID1B is associated with poor prognosis and chemotherapy resistance in epithelial ovarian cancer. Tumour Biol 2015;36:2465-72.
90. Salminen A, Kaarniranta K, Kauppinen A. Hypoxia-Inducible Histone Lysine Demethylases: Impact on the Aging Process and Age-Related Diseases. Aging Dis 2016;7:180-200.
91. Chicas A, Kapoor A, Wang X, Aksoy O, Evertts AG, Zhang MQ, *et al*. H3K4 demethylation by Jarid1a and Jarid1b contributes to retinoblastoma-mediated gene silencing during cellular senescence. Proc Natl Acad Sci U S A 2012;109:8971-6.
92. Sikora E, Bielak-Zmijewska A, Mosieniak G. Cellular senescence in ageing, age-related disease and longevity. Curr Vasc Pharmacol 2014;12:698-706.
93. Greer EL, Maures TJ, Hauswirth AG, Green EM, Leeman DS, Maro GS, *et al*. Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in *Caenorhabditis elegans*. Nature 2010;466:383-7.
94. Li L, Greer C, Eisenman RN, Secombe J. Essential functions of the histone demethylase lid. PLoS Genet 2010;6:e1001221.
95. Booth LN, Brunet A. The Aging Epigenome. Mol Cell 2016;62:728-44.
96. Wynder C, Stalker L, Doughty ML. Role of H3K4 demethylases in complex neurodevelopmental diseases. Epigenomics 2010;2:407-18.
97. Shen E, Shulha H, Weng Z, Akbarian S. Regulation of histone H3K4

[Downloaded free from http://www.ejcrp.org on Thursday, June 4, 2020, IP: 10.232.74.23]

methylation in brain development and disease. Philos Trans R Soc Lond B Biol Sci 2014;369: pii: 20130514.
98. Athanasakis E, Licastro D, Faletra F, Fabretto A, Dipresa S, Vozzi D, *et al*. Next generation sequencing in nonsyndromic intellectual disability: From a negative molecular karyotype to a possible causative mutation detection. Am J Med Genet A 2014;164A: 170-6.
99. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, *et al*. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014;515:209-15.
100. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, *et al*. The contribution of de novo coding mutations to autism spectrum disorder. Nature 2014;515:216-21.
101. Vallianatos CN, Iwase S. Disrupted intricacy of histone H3K4 methylation in neurodevelopmental disorders. Epigenomics 2015;7:503-19.
102. Miolo G, Giuffrida MG, Corona G, Capalbo A, Pivetta B, Tessitori G, *et al*. A novel mosaic 1q32.1 microduplication identified through Chromosome Microarray Analysis: Narrowing the smallest critical region including KDM5B gene found associated with neurodevelopmetal disorders. Eur J Med Genet 2019;62:103558.
103. Turgeon PJ, Sukumar AN, Marsden PA. Epigenetics of cardiovascular disease – A new "beat" in coronary artery disease. Med Epigenet 2014;2:37-52.
104. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol 2015;89(Pt B): 122-35.
105. Fork C, Gu L, Hitzel J, Josipovic I, Hu J, SzeKa Wong M, *et al*. Epigenetic regulation of angiogenesis by JARID1B-induced repression of HOXA5. Arterioscler Thromb Vasc Biol 2015;35:1645-52.
106. Wu L, Cao J, Cai WL, Lang SM, Horton JR, Jansen DJ, *et al*. KDM5 histone demethylases repress immune response via suppression of STING. PLoS Biol 2018;16:e2006134.
107. Blair LP, Cao J, Zou MR, Sayegh J, Yan Q. Epigenetic Regulation by Lysine Demethylase 5 (KDM5) Enzymes in Cancer. Cancers (Basel) 2011;3:1383-404.
108. Hong X, Kim ES, Guo H. Epigenetic regulation of hepatitis B virus covalently closed circular DNA: Implications for epigenetic therapy against chronic hepatitis B. Hepatology 2017;66:2066-77.
109. Liu X, Secombe J. The histone demethylase KDM5 activates gene expression by recognizing chromatin context through its PHD reader motif. Cell Rep 2015;13:2219-31.
110. Vogel FC, Bordag N, Zügner E, Trajkovic-Arsic M, Chauvistré H, Shannan B, *et al*. Targeting the H3K4 demethylase KDM5B reprograms the metabolome and phenotype of melanoma cells. J Invest Dermatol 2019;139:2506-16.e10.
111. McElroy GS, Chandel NS. Probing mitochondrial metabolism *in vivo*. Proc Natl Acad Sci U S A 2019;116:20-2.
112. Huang Y, Vasilatos SN, Boric L, Shaw PG, Davidson NE. Inhibitors of histone demethylation and histone deacetylation cooperate in regulating gene expression and inhibiting growth in human breast cancer cells. Breast Cancer Res Treat 2012;131:777-89.
113. Wang H, Song C, Ding Y, Pan X, Ge Z, Tan BH, *et al*. Transcriptional regulation of JARID1B/KDM5B histone demethylase by Ikaros, histone deacetylase 1 (HDAC1), and casein kinase 2 (CK2) in B-cell acute lymphoblastic leukemia. J Biol Chem 2016;291:4004-18.
114. Liu X, Greer C, Secombe J. KDM5 interacts with Foxo to modulate cellular levels of oxidative stress. PLoS Genet 2014;10:e1004676.
115. Ratan RR. Epigenetics and the nervous system: Epiphenomenon or missing piece of the neurotherapeutic puzzle? Lancet Neurol 2009;8:975-7.
116. Berdasco M, Esteller M. Clinical epigenetics: Seizing opportunities for translation. Nat Rev Genet 2019;20:109-27.
117. Sayegh J, Cao J, Zou MR, Morales A, Blair LP, Norcia M, *et al*. Identification of small molecule inhibitors of Jumonji AT-rich interactive domain 1B (JARID1B) histone demethylase by a sensitive high throughput screen. J Biol Chem 2013;288:9408-17.
118. Zheng YC, Chang J, Wang LC, Ren HM, Pang JR, Liu HM. Lysine demethylase 5B (KDM5B): A potential anti-cancer drug target. Eur J Med Chem 2019;161:131-40.